RISK FACTOR RESEARCH IN THE MAJOR MENTAL DISORDERS

Proceedings of a Conference, April 3-4, 1980

U. S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Alcohol, Drug Abuse, and Mental Health Administration

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RISK FACTOR RESEARCH IN THE MAJOR MENTAL DISORDERS

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Edited by
Darrel A. Regier and Gordon Allen

U. S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Alcohol, Drug Abuse, and Mental Health Administration

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FOREWORD

During an era of medical and public health revolutions, mental and emotional disorders have not proven susceptible to innoculation, nutrition, improved sanitation, or other measures which effectively have addressed other major health problems. Unlike many once-crippling infectious diseases, the etiologies of mental disorders are multifactorial, and the search for risk factors must not only be directed toward but must also find pieces of the solutions in such diverse fields as biochemistry, genetics, psychology, demographics, and combinations thereof.

The mental health research community has not shirked this imposing task. Arduously, over the years, researchers have put together the pieces of the puzzle. Hypotheses have been proposed, discounted, and added to the knowledge base which has accumulated steadily, affording ever greater reliability.

The meeting that yielded this volume was conceived in the summer of 1979 and convened the following Spring. It occurred at the end of an exciting decade of research in mental health--and at the beginning of what proves to be an even more exciting decade. Unprecedented technologies in the basic research laboratories, innovative approaches to the study of developmental factors that would suggest either resistance or capitulation to stress, and methodologies to conduct increasingly valid epidemiologic studies all have converged within recent years. Individually, each of these will and already are contributing to our understanding of the brain, to therapeutics, and to the development of early identification and intervention strategies.

Early intervention and prevention of mental disorders will remain among the foremost researh objectives of the National Institute of Mental Health. In that spirit, we are pleased to make Risk Factor Research in the Major Mental Disorders available to the scientific community.

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PREFACE

The conference summarized in this report was organized cooperatively by three divisions of the National Institute of Mental Health (NIMH), mainly for immediate guidance in planning intervention research and epidemiologic surveys. From the start, however, we believed that the proceedings should be made more widely available and permanently recorded as a reference point for future planning in risk factor research.

The cooperating units of NIMH were the Division of Biometry and Epidemiology (DBE), the Division of Extramural Research Programs (DERP), and the Intramural Research Program (IRP). Within DBE, the editors and William Eaton played the most active roles. In the other two divisions, a number of scientists made useful recommendations, but Robert Hirschfeld and Monte Buchsbaum agreed to contribute papers and were also brought directly into the detailed planning. The Fogarty International Center made available its spacious and elegant meeting facilities on the grounds of the National Institutes of Health in Bethesda.

We wanted the formal papers to be circulated in advance, and about half of them were. The oral presentations were abbreviated to allow almost equal time for immediate discussion. Ten of the formal papers occupied the first day of the meeting, while Dr. Gruenberg's paper was scheduled as an introduction to the "workshop" sessions on the second day. Here, Dr. Gruenberg's paper appears first, but the discussion which followed it is placed at the end of the formal sessions, in its original context.

In summarizing the discussions we have taken the liberty of giving most coverage to the aspects and ideas that best relate to our objectives. Scientific content and such issues as criteria for inclusion of risk factors are presented in more detail than are the debates over mode of research support or over appropriateness of particular risk factors.

Also in the interest of brevity, most of the contributing authors were asked to shorten their manuscripts, some to a painful degree. All were urged to restrict bibliographic references to a minimum and to cite their own previous papers when these were useful in guiding readers to the more specialized literature.

It is nearly impossible to attach a name to each significant datum or idea represented in the summarized discussions. The transcript recorded virtually every listed participant as playing a useful role and so deserving partial credit for whatever value these proceedings may have.

Darrel A. Regier
Gordon Allen

CONTENTS

Foreword iii

Participants v

Preface ix

I. INTRODUCTION: 1-19

Welcoming Remarks
HERBERT PARDES 3

Statement of Objectives
DARREL A. REGIER 5

Risk Factor Research Methods
ERNEST M. GRUENBERG 8

II. THE DEPENDENT VARIABLES: MAJOR MENTAL DISORDERS: 21-107

The Current Status of Research with Children at Risk for Schizophrenia and Other Forms of Psychopathology
NORMAN GARMEZY 23

Biological Risk Factors in Schizophrenia
SEYMOUR S. KETY and DENNIS K. KINNEY 41

Psychosocial Risk Factors for Depression
ROBERT M.A. HIRSCHFELD and CHRISTINE K. CROSS 55

Somatic Findings in Affective Disorders: Their Status as Risk Factors
ARTHUR J. PRANGE, JR., and PETER T. LOOSEN 69

Risk Factors in Anxiety Disorders
ISAAC MARKS 81

Risk Factors and Personality Disorders
RONALD L. MARTIN and SAMUEL B. GUZE 95

III. THE INDEPENDENT VARIABLES: SOME BROAD RISK FACTORS: 109-176

Demographic and Social-Ecologic Risk Factors for Mental Disorders
WILLIAM W. EATON 111

Life Stress and Psychopathology
BARBARA SNELL DOHRENWEND and BRUCE P. DOHRENWEND 131

Genetic Vulnerability in Psychiatric Epidemiology
ELLIOT S. GERSHON 145

The Biological High-Risk Research Strategy: A Review of Recent Studies
ROBERT D. COURSEY and MONTE S. BUCHSBAUM 163

IV. INTERACTION AND CONCLUSIONS: 177-203

Working Group on Genetic, Biochemical and Physiological Risk Factors . 179

Working Group on Psychological and Socioenvironmental Risk Factors . . 182

Large-Group Discussion 185

Concluding Remarks
GERALD L. KLERMAN 189

Editors' Summary 193

GLOSSARY OF ACRONYMS 205

INDEX 207

I

INTRODUCTION

WELCOMING REMARKS

Herbert Pardes, M.D.

Director
National Institute of Mental Health

INTRODUCTION

I am delighted that all of you could join us here today. We appreciate your willingness to leave your busy schedules to participate in this 2-day NIMH conference on risk factors in mental disorders.

For more than 30 years, the Institute has supported and conducted research to determine the causes of mental disorders. The present is a particularly important and, in a sense, an exciting time, despite the fact that there has been both a chronic and, as you know, a rather acute concern about broad economic issues which, in turn, have ramifications for support of mental health programs.

But it is noteworthy that NIMH, which from 1968 to 1976 actually experienced a decline in its research support budget—at a time when many of the other institutes in the NIH were moving rapidly ahead in terms of fiscal support—now has an opportunity to regain and further expand its research capacity. In the last 5 years, that is, 1977 through to the President's projected 1981 budget, we have experienced a dramatic increase in research support for NIMH. The increase through 1980 is approximately 55 percent, and, if the President's budget were endorsed by the Congress for 1981, the research budget increase would total 70 to 75 percent over the period of the last 5 years.

The comparison of an 8-year period in which the budget declined in actual dollars and a 5-year period in which the budget went up by over three-quarters of the 1976 base clearly represents an opportunity, and the opportunity was very much needed. In the previous 8 years, the mental health field, the research field, had suffered dramatically from an absence of support. I hasten to add that the present level of support still leaves us below, considerably below, our buying power of 1969. There still is a distance to go, but the fact remains that opportunities are opening up again in the field of mental health research.

In the last few years, research has shown increasing promise for demonstrating the importance of hereditary and biological risk factors for some of the more severe affective and schizophrenic disorders. We still have much to learn about the relative roles of an array of factors—biological, psychological, and social—which contribute to the etiology of these disorders, as well as personality disorders, anxiety states, etc.

This conference offers us a useful opportunity to review some of the progress over the last 30 years before we embark on yet new research projects designed to determine the relative contribution of various risk factors to the development of mental disorders. New case-identification methods for field surveys in mental health have opened up a new avenue for assessing the contribution of multiple risk factors. Moreover, the implications of new data derived from these studies for preventing future mental disorders have not been lost on the Institute.

At the urging of the President's Commission on Mental Health, the Institute recently embarked on a major new initiative in prevention. We established an office with primary responsibility for the program, and we have begun to develop research on such issues as the impact of marital disruption on children and the impact on the nuclear family of the occurrence of severe alcohol, drug, or mental disorders among parents. We have gained a great deal of focus, a great deal of attention, a great deal of advice, a great deal of input with regard to our prevention program.

Our research strategy is critical, for, when we are still questioning some of the proof of the efficacy of our existing psychiatric services, it is necessary that we first make sure of exactly what we know before we start launching any kind of new endeavor. We must be certain that new programs in prevention have an empirical foundation. Research must focus on all approaches and channels that offer a reasonable promise for improving our prevention effectiveness.

We are pushed continually as to how soon we can have our preventive approaches and services available and operating in communities throughout the Country. I want to emphasize that we plan to proceed with as solid a foundation as possible, and we look to you to help us with advice on how to embark in that fashion.

The program for this meeting was organized by several different components of the NIMH. They include the Division of Biometry and Epidemiology, the Division of Extramural Research Programs, and our Intramural Research Program. This reflects the pervasive interest within NIMH in the question of risk factors and in identifying the appropriate directions to move in the field of prevention.

STATEMENT OF OBJECTIVES

Darrel A. Regier, M.D., M.P.H.

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I would first like to provide a brief background concerning the Institute's interest in convening this conference and then restate our objectives. Some of these objectives are shared among several NIMH divisions, and accordingly the conference is sponsored jointly by the Division of Biometry and Epidemiology, the Division of Extramural Research Programs, and the Intramural Research Program. Staff from all three areas have helped to plan the conference and have enhanced its quality with their contributed papers.

First, on behalf of the Division of Biometry and Epidemiology, I will review the development of our interest in risk factor research.

Survey techniques for the epidemiologic study of mental disorder were successfully applied in several major studies of the 1950s, such as the Midtown Manhattan and Stirling County studies. They led to the concept of field stations for epidemiologic research under NIMH sponsorship. Two such field stations were organized in 1967-68 by the NIMH Center for Epidemiologic Studies, one in Kansas City and one in Washington County, Maryland.

In 1976, through the efforts of Morton Kramer, Director of the Biometry Division, that division and the Center for Epidemiologic Studies joined to form the Division of Biometry and Epidemiology. In the same year, Ben Locke, Chief of the Center for Epidemiologic Studies, suggested a new series of epidemiologic studies using CMHC catchment areas as geographically defined denominator populations. The term, Epidemiologic Catchment Area, was coined to describe such studies.

In discussions within the division we decided that our future epidemiologic studies should identify not isolated mental or emotional symptoms but recognizable mental disorders as viewed by service providers. The work of Myrna Weissman and Jerome Myers at Yale demonstrated that it was possible to use a structured psychiatric interview to obtain diagnoses based on the Research Diagnostic Criteria in a community survey.

The New Haven study used instruments that were developed with the support of the Institute's intramural and extramural research programs, the Schedule for Affective Disorders and Schizophrenia (SADS) and its lifetime version, SADS-L.

Large-scale studies, however, require an instrument that can be used by lay interviewers who have considerably less training than did those who made the Yale survey. We therefore arranged a conference in 1978 to review case-identification methods then available. We wanted to develop an instrument for field studies, using lay interviewers, that could accommodate as many as possible of the DSM-III diagnoses, the Research Diagnostic Criteria (RDC) diagnoses, and the Feighner criteria diagnoses. As a result of the conference, Lee Robins at Washington University of St. Louis was commissioned to develop such an instrument, which was named the NIMH Diagnostic Interview Schedule (DIS).

While Dr. Robins was developing the DIS, we were initiating our Epidemiologic Catchment Area (ECA) Program. These surveys were to include the DIS, the identification of life events, other sociodemographic variables related to the development of mental disorders, and characteristics that would define the use of services and barriers to service, such as the stigma of mental illness. The design called for sampling of individuals in households and in institutions in a population of at least 200,000, and conducting interviews with about 3,500 people at each site. Following the first wave of interviewing, there would be at least one followup a year later to obtain incidence data and information on service use.

We funded the first site, at Yale University, in September of 1978. In the fall of 1979, The Johns Hopkins University and Washington University of St. Louis were successful in qualifying as additional sites.

The primary aim of the ECA Program is to measure the scope of the mental health problem and the use of services for patients with different disorders and according to other characteristics. A second goal is to identify patient characteristics or environmental factors which place certain individuals at greater risk of developing disorders and of using available services. The present ECA Program does not go far enough toward the second goal, and another generation of population studies may be needed to advance our understanding of multiple causation and suitable intervention strategies beyond that achieved through our current design.

That is the background for our division's interest in risk factor research. The Divisions of Intramural and of Extramural Research are interested in the subject matter first, because they are actively engaged in doing or supporting such research and, second, because any new instrument or predictor of mental illness may improve their research design or increase the homogeneity of their study samples. The three divisions also have a common interest in case-identification instruments which clearly define the dependent variables, that is, the clinical diagnoses of our research subjects.

Let me now state our objectives in precise terms. Risk factors should identify population subgroups in which specific disorders will be concentrated, but the variables available to psychiatric epidemiologists now do not go much beyond traditional demographic variables and life events. We need both socioenvironmental and psychological variables with higher specificity for the major mental disorders, and we also want guidance in choosing biological variables to incorporate in epidemiologic studies.

A second objective in reviewing risk factors is to assess the potential utility of each of them in trials similar to the Multiple Risk Factor Intervention Trials (MRFIT) program that has been so successfully mounted by the Hert Institute.

A third objective, particularly important if we are disappointed in the first two objectives, is to develop criteria for deciding when a potential risk factor should be subjected to a large-scale epidemiologic trial.

Finally, we hope to promote a closer alliance between neurobiology and general psychiatry, sociology, and psychology in research on the etiology of mental disorders. With much to accomplish and with a wide spectrum of experts in attendance, we welcome all of you to what we hope will be a stimulating and productive exchange of ideas.

RISK FACTOR RESEARCH METHODS

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INTRODUCTION

This sketch of risk factor research methods is an attempt to show that biostatisticians and epidemiologists have accumulated techniques for determining basic risk measurement. It reviews the relevant literature as an introduction to, not a substitute for, the publications cited.

Epidemiological research on risk factors has a tradition. One feature of that tradition is a readiness to switch levels to pursue a problem. One may get into a problem with a psychological hypothesis, but, in pursuing the problem, one may have to switch to interest in some DNA molecules or some brain tissue changes or the social network theory. When the evidence points away from the originally suspected antecedent there are three choices: drop the problem because it is outside the investigator's "discipline," learn more about the nature of the apparent risk factor, or (if one does not wish to keep acquiring new doctorates) learn to collaborate. Epidemiology has a tradition of collaboration; it progresses by integrating its hypotheses and research with clinical, laboratory and biostatistical research workers.

Today, to facilitate interdisciplinary collaboration, we must all learn about risk research methods, whether we want to or not. We cannot leave it to the "riskologists."

Epidemiology is a Greek word for a science. As Hippocrates used it, the word means the study of "upon the people." It is the study of how things fall on the people. A disease that strikes the people in one place at a particular time is an epidemic. But epidemiology is not just the study of epidemics (as Webster would have you believe). It is more generally the study of:

- Who gets sick, and who doesn't get sick?
- Why? (What are the risk factors?)
- What can we do to make the sickness less common?

So epidemiology is the basic science of public health practice and preventive medicine. It is an action science, directed at a set of practical problems. Many useful epidemiologic studies do not lead directly to action. But the goal of epidemiologic inquiries is to find a modifiable risk factor, a risk factor that can be manipulated through social action or individual action so as to **lower the frequency** of a disease, of a disability, or of death.

Hence, epidemiology is pursued in the Public Health Service and in State and city health departments. One cannot help being an epidemiologist, if one is interested in disease prevention. Actuarial methods are designed to get an accurate measure of contingency risks. Epidemiologists are preoccupied with finding ways to lower the risk of people becoming ill or disabled or dead. Epidemiology is defined by its questions, not by its method of getting answers.

Epidemiology does not try to go it alone. Many contributions to mental disorder epidemiology have been made by nonepidemiologists who insist they were doing something else. For example, H. Warren Dunham (6) insists he was doing social ecology research in Mental Disorders in Urban Areas. Also, Seymour Kety has been doing risk factor research in his adoption studies, although that is not his term for it.

QUANTIFICATION OF RISK

The concept of risk is older than the idea of measuring risk. People took chances; they did not say how big the chance was. Being a sailor was a risky occupation, sending a ship from England to Italy was risky. Everyone knew it was dangerous, but no one put a numerical value on the risk. Risk became something to measure, when people tried to insure themselves against risk. Risks were assigned numerical values as a result of bargaining between those who took the risk and those who would pay. The ship owner bet the ship would sink; the insurer bet it was going to survive the trip. They had to agree on odds. How much does the ship owner pay the insurer (the premium) so the insurer will pay the owner the cash value of the ship and its cargo (the benefit) if the ship sinks? They negotiated until they made a deal. The ratio of premium to benefit quantifies the size of the risk.

Each side guessed. It was a betting proposition. This went on for a long time in risk measurement. The whole life insurance business is built on it. Actuarial statistics try to state how many people out of a cohort are going to die so as to guide those who sell life insurance or annuities.

Until the time when the National Institutes of Health were created, almost all statistical methods of figuring odds and chances about health were based on the risk of dying.

Individual Risk

J.N. Morris (16) describes individual risk in his text, Uses of Epidemiology. The risk of dying is higher for the very fat (or the very lean) than for the average-weight person. At different ages, people are at different risks of having automobile

accidents. An outstanding example of measured individual risk is the well-established fact that the risk of a woman's newborn baby having Down's syndrome rises exponentially with the mother's age.

One way of measuring the individual risk of some particular event by a particular age is a simple summation of the accumulated experience over time of age-specific incidence rates of that event. (The annual incidence rate is the number of new cases starting in a year divided by the average number of people observed during that year.) Measurement of the accumulated risk in time, or individual risk as a function of age, is illustrated by a study of senile dementia. The probability that a man who survives to a given age will have escaped the clinical signs of senile dementia (Alzheimer's Type) is given in table 1.

Table 1. Effects of age as a risk factor in developing senile dementia, Alzheimer's type, in male subjects (19).

Age	Proportion Unaffected
60	1.00
70	.97
75	.93
80	.83
85	.71

This summary of longitudinally gathered data counted the number of individuals who have survived to each age and who have escaped the development of a particular condition. The proportion who escaped, of course, gives, by subtracting from one, the proportion who had developed it. This use of a life-table technique is particularly valuable when one is interested in the long-term risks of developing a condition. This way of organizing information tells us the effect of age as a risk factor. With such a summary, it is then possible to divide the cohort of observed individuals into two parts according to a given suspected "risk factor" and determine whether the risk for one group is higher than for the other. This type of analysis is necessary in this example for two reasons. First, age is a known powerful risk factor, and we wish to discount its effect when seeking to identify other risk factors. Second, death is a powerful outcome competitor in the population, and we do not want its determinants to confound our search for the determinants of SDAT.

Contingency Risk

A familiar example of a simple contingency risk, as presented in table 2, would be the increased risk which a person with a history of previous mental hospital admission has of being admitted during the next 2 years to a mental hospital. The insurance companies will charge you more for your automobile insurance if you have a history of accidents.

These are examples of the principle that a person's past experience is the best predictor of that individual's future experience in the absence of any other information.

"Nothing fails like failure and nothing succeeds like success."

Table 2. A simple contingency risk.

	With C	Without C
With R	a	b
Without R	c	d

R = risk factor which is being studied

C = condition which the risk factor is suspected of favoring

Obviously, if R is in fact a risk factor for C, **a**/(**a** + **b**) will be larger than **c**/(**c** + **d**). For any single set of research data, the probability that such a finding is due to chance sampling will be measured by the "significance test." But the significance test is not a useful indicator of how strongly R affects the frequency of C; for that, something more is needed.

Relative Risk

How much risk does cigarette smoking produce for coronary deaths and how much for lung cancer deaths? Which is the greater risk? Clearer concepts of risk quantification emerged from efforts to interpret data which were not directly related to this question.

Cornfield (5), in 1951, introduced the precise concept of relative risk—the incidence of disease in an exposed group divided by the incidence of disease in a nonexposed group. It measures how much the risk factor affects incidence rates. Relative risk can also be defined in terms of conditional probabilities, which is the way in which Armitage (1) and Fleiss (7) discuss it.

Cornfield was interpreting case-control data. He imagined the existence of a suitably representative sample of people about whom **a**, **b**, **c** and **d** in table 2 are all known on a prospective basis. That is, (**c** + **d**) and (**a** + **b**) had been identified in the past, and the values of **a** and **b** were observed as the cases developed.

He then introduced the concept of relative risk to show how case-control data from retrospective studies could be used to **estimate** the value of a relative risk, given certain assumptions. In a case-control retrospective study the new cases arising from a population (**a** + **c**) are identified and a group of comparable controls (**b** + **d**) are identified;

then data are obtained retrospectively as to which cases and which controls had previously been exposed to R. He showed that the "odds ratio," which is the ratio of cross products, **ad/bc**, is a good estimate of the relative risk. His paper ended as follows:

> The results of even the most carefully analyzed set of such data may be open to question, and **these doubts can be resolved only by methods of data collection that provide representative samples of diseased and nondiseased persons** (5, emphasis added).

Excellent discussions of the odds ratio approach to relative risk estimates and the value of the logit as developed by Haldane (11) are to be found in Fleiss (7) and in Lilienfeld (13). The logit expression of relative risks makes it possible to examine the interaction of risk factors quantitatively so as to estimate the total risk resulting from clusters of risks. (Lilienfeld's second edition appeared after this paper was given and contains detailed discussions of most of the risk-measurement concepts in this paper.)

The Prospective Design

As indicated above, Cornfield (5) imagined a prospective study when he defined relative risk. If the data are gathered prospectively, the relative risk is the ratio of

$$\frac{a}{a+b} \quad \text{to} \quad \frac{c}{c+d} \ .$$

Thus, Cornfield's relative risk is measured directly rather than estimated. If the condition being studied is not common, both **a** and **c** are small while **b** and **d** are large. This is thought to be inefficient. A great deal is spent finding out the ratio of **b** to **d** without adding greatly to the findings. A prospective study is also inefficient if many years elapse between R and C.

However, if the condition is fairly common, a prospective design can be seriously considered. For example, it makes sense to study factors associated with rehospitalization after leaving a psychiatric inpatient service, if the psychiatric inpatient service readmission probability is about 50 percent within a reasonable time period (6 months to a year). If one wishes to find what kinds of risk factors are associated with the readmission, a prospective design of a cohort of releases would not take an unreasonable amount of time, and the data regarding the risk factors can be gathered while the stream of patients is followed in the community.

The Nonconcurrent Prospective Design

The prospective study selects two populations (with R and without R) and follows them forward in time to find out who develops C. It measures the relative risk directly. It takes a long time and, unless the condition is very common, a large number of subjects.

The nonconcurrent prospective study saves time. It locates an old record of exposure to R in a population some time in the past, then locates the subjects at present, and sorts them into cases and noncases. Such studies are becoming more and more common in general epidemiology risk factor research but are not frequent in mental disorder risk factor research.

Stein and Susser et al. (21) tried to use the Nazi-imposed famine in certain districts of Holland during World War II as a means of determining whether a sharp reduction in maternal diet affected the mental development of the children born in succeeding months. There is significant question as to whether the "experiment" fit the needed design and whether the gathered data were appropriate to the hypothesis. But it was an attempt to do a nonconcurrent prospective study.

The Case-Control Retrospective Design

The case-control study is extremely suitable as a first stage of investigation when the risk factors suspected are many and can be ascertained through histories.

For a case-control study, it is necessary to systematically monitor the new cases of the condition arising in a population over a specified time period. This is usually done through a medical care record system which presumably has an adequate casefinding and recording mechanism. The frequency of the suspected risk factor or risk factors is ascertained for each case. A group of **comparable** controls is simultaneously identified and the same suspected risk factors ascertained for them. If the condition being studied is of a low frequency, this method provides a good approximation to relative risk, as Cornfield has pointed out, in the form of the odds ratio, (a x **d** / **b** x **c**).

The weakness of this method must be kept in mind. The identification of a comparable population, which differs from the cases only in that they do not have the condition, can rarely be accomplished with confidence. It is customary to take a group of cases with another condition in the same medical care facility, but there can be a systematic bias for the other condition with respect to the use of that medical care facility by the population from which the cases have been drawn. Nonetheless, the method has great power and economy.

Problems arise in ensuring that the ascertaining of the risk factors is done by the same methods in both cases and controls. For example, if the interviewer believes that cigarette smoking causes lung cancer and knows which subjects have cancer, the interviewer might probe with more vigor a history of no cigarette smoking in the cancer cases than in the controls. If the interviewers and subjects can be blind as to the way in which the sample was drawn and the reason for asking about the risk factors, much of this bias can be removed.

The most influential series of case-control studies on mental disorders were initiated by Parkhurst (14) and Lilienfeld (14,15,18) and pursued by them and Pasamanick (15,17,18) and Knobloch (17) regarding the "continuum of fetal damage" in obstetrical complications. This series of investigations linked mental retardation, epilepsy, reading disability, and impulsive behavior disorders to a wide variety of obstetrical complications. They have not been followed by appropriate prospective investigations starting with obstetrical complications and following the offspring through the years to enumerate the full range of consequent disorders.

Many case-control studies have been done in an effort to identify antecedent factors or current factors in such conditions as schizophrenia. Most studies have had inappropriate controls. Too often the controls have been hospital employees or students from a social background altogether different from the patients'. Biochemical studies have not controlled diets. It cannot be emphasized too strongly that the careful selection of comparable controls is the heart of the case-control investigation, if it is not to be misleading.

The Epidemiologic Catchment Area (ECA) Project

Clinical cases do not make good samples for case-control risk factor research, mainly because every clinical sample has some special selection bias which one can never be sure has been reproduced in the controls. A model data source for case-control studies is provided in the ECA surveys of prevalence of mental disorder, currently supported by the NIMH. The prevalence surveys are taken in representative samples of area populations and repeated on the same subjects 1 year later with a resurvey to detect newly arisen cases.

Prevalence data from these morbidity surveys (how many people are sick at one time) can be used in case-control studies, drawing controls from the same surveyed population at the same time by the same methods. But incidence data (how many got sick during the year) are superior for detecting a risk which is associated with onset of a disorder. Some conditions may be frequent enough in the ECA surveys to permit retrospective case-control studies based on new cases only.

Prevalence rates tend to be equal to the product of incidence rates times the average duration of each episode. So case-control studies based on prevailing cases may give clues to risk factors without differentiating those which increase the risk of developing a condition from those which make each episode likely to last longer. For example, effective medical treatment can work to either lower or raise prevalence rates without affecting incidence rates. It can shorten the duration of high blood pressure episodes or of depressive episodes. Or it can lengthen the duration of Down's syndrome or senile dementia (9).

The ECA surveys will give us the best samples anyone has ever had for mental disorder case-control retrospective studies. The Hopkins-based East Baltimore survey will be most valuable because each case and each control will have had a clinical reappraisal which will remove false positives and false negatives from the sample.

Attributable Risk

Morton Levin (12) asked a different question about the importance of a risk factor: "What portion of lung cancer would disappear from the population if everybody stopped smoking cigarettes?" He used relative risk data to estimate how much of the lung cancer would disappear if you took away the cigarettes, that is, the proportion of cases one can attribute to cigarette smoking. This is an important quantity.

If **b** is the proportion of the general population exposed to **r**, then **S**, the attributable risk is

$$S = \frac{b(r-1)}{b(r-1) + 1}$$

where **r** is the relative risk as defined above. Case-control designs can provide estimates of **S** to the extent that they provide good measures of **b** and of **r** (13).

Prospective designs give more direct measurements of **r**, but they also provide no direct measurement of **b**, unless the controls are representative of the general population in their rates of exposure to **R**. Attributable risk can be measured directly if a preventive trial is conducted.

Risk Measures From Preventive Trials; Historical Examples

The prevention of pellagra among institutional inmates was a dramatic investigation started in 1913 (8). It apparently prevented new cases of pellagra from arising by improving and supplementing diets.

The report leaves something to be desired because no relative risk figures were published. They did not systematically tabulate the risk of developing pellagra among the controls. Instead, they pointed out that the death rate in the communities surrounding the orphanages and mental hospitals continued to be high for pellagra. In such instances, a preventive trial related to a key risk factor can provide such dramatic evidence that subtle quantification of relative risk becomes an example of "misplaced precision."

The Newburgh-Kingston (2) Fluoridation Experiment lasted from 1945 to 1955. The experiment was organized largely by the New York State Health Department but required a great deal of collaboration with other agencies. The survey examined children's teeth in the two cities. Fluorides were added to the water supply of Newburgh in 1945. Children's teeth were surveyed from both cities for 10 years.

The results were conclusive. The frequency of cavity-free mouths in the children who grew up in Newburg was much higher than the frequency of cavity-free mouths in the children who grew up in Kingston. It was established that adding of fluoride to a city's water supply was a safe, effective way of reducing dental caries. Low fluoride-content drinking water is a risk factor for dental decay. The preventive trial showed that most decay could be attributed to low fluoride concentrations in the water.

Neither of these preventive trials randomly assigned individual subjects to the preventive and control groups. Whole populations were assigned because the preventive intervention was conceptualized around a community-based resource—food or water. In an era when the double-blind, randomized clinical trial is riding high, we should remind ourselves that other designs still have their use.

The Dutchess County Preventive Trial of the Chronic Social Breakdown Syndrome (3) began in 1959. Based on Hudson River State Hospital in Poughkeepsie, N.Y., the experiment reformed the care of seriously mentally ill patients who had been entering a large mental hospital admission service with later transfer to a specialized chronic service or discharged.

The reform created a Dutchess County service with its own buildings and staff. All Dutchess County cases, new and old, were cared for in this service. It was a very active, acute care program which released patients from hospital as early as possible following admission and continued to provide care to them in the community. It was assumed that first admission rates and readmission rates would rise. Would there be a decline in the rate at which new cases of chronic deterioration in personal and social functioning were developing?

A decline was anticipated because of the following program features: the systematic effort to preserve the patient's assets during the initial hospitalization, the assiduous efforts made to preserve his social support systems and community support systems, and the speedy efforts to re-relate the individual as rapidly as possible to the existing social support sytem and community support systems. The continuing availability of the hospital-based clinical team (with easy brief readmission) was considered a means of preventing community and family rejection in cases of chronic or recurring psychosis. Hence, a rise in readmission rates was seen as a means of achieving the end: reduction of the risk of Chronic Social Breakdown Syndrome (CSBS).

The part of the hospital used for this experiment had no locked services and no visiting restrictions. Compulsory hospitalization was avoided by seeking the patient's active cooperation from the very first contact and by providing precare consultation by hospital psychiatrists to anyone contemplating sending a patient to the State hospital. It was assumed that the frequency of acute episodes of psychotic decompensation would not decrease in the general population. Because there was fear that the new pattern of care might lead families to keep patients at home or to send them elsewhere when they became troublesome, all residents of the county between the ages of 16 and 65, who had been in any of kind of inpatient psychiatric service after 1955, were surveyed annually to ascertain the frequency of CSBS.

Because the program had to be introduced for the entire county or not at all, there was no way of getting a comparable control on a random basis. A matching community, as in the Kingston/Newburgh study, was not practicable. The only control arose from the before-and-after observations. Between 1960 and 1963, the annual number of new cases of severe CSBS which arose in this population of 100,000 declined from something over 45 to something under 16 per year, a drop to less than one-third of the previous rate. The rates of recovery from this chronic syndrome were the same, regardless of the year of onset, so that the change could be attributed to the rate of recovery in the first year (actually, probably in the first half year). Thus, the risk of developing a CSBS dropped from 45 to 15 per 100,000 per year; so about 30 new cases of CSBS per 100,000 per year could be attributed to the old system of care. The attributable risk was then 67 percent.

The findings of this study (when attended to at all) tend to be interpreted to mean that it is justifiable to abandon chronic patients by discharge from mental hospitals into inadequate community-care programs under the slogan of "deinstitutionalization." (10) It is rarely recognized that these services were, in fact, provided by a reorganization of existing services, techniques, and personnel from a State mental hospital with the continuing availability of the hospital and its staff to patients, family, and community.

New Opportunities For Preventive Trials

Several theories regarding risk factors with respect to mental disorders are now ripe for preventive trials.

The relation of maternal malnutrition (20) to central nervous system development before birth remains cloudy. While there are various programs in existence to raise the nutritional status of marginally nourished young women in this country and elsewhere, none of them is applied with sufficient intensity to get to all of the young women at risk of having a child damaged because of inadequate nutrition of the mother. It certainly

would not do such young women any harm if they were systematically educated to feed themselves better and were provided with the nutritional supplements necessary for optimal nutrition.

Such experiments have been tried, but they share one deficiency. From the available evidence, it would be important to start improving the nutrition of the treated group of young women long before they became pregnant in order to assure that they had excellent reserves of the essential nutrients at the time they became pregnant. This would require artful community organization and education programs and not just the erection of a scientific design.

Widow-to-widow (23) counseling has been fashionable as a method of improving the handling of grief and, presumably, preventing psychosomatic and depressive complications. But, so far, no program has been set up on a preventive trial design with appropriate controls, and no data are available as to how much these programs reduce the risk of specific disorders. Meanwhile, there is pressure to expand the programs. If these programs are truly effective, they should be expanded much more quickly. If they are not effective, they should not be supported in the name of prevention.

Emily Broussard (4) identified a syndrome of poor emotional development in daughters of women who, when they were pregnant, had low self-esteem. There is an easily administered screening test to locate such women in prenatal clinics and obstetrical services, and there is a reeducation program designed for them. An objectified screening device to locate the children whose emotional development has been damaged needs to be developed. A preventive trial is indicated, even at this early stage of knowledge. It is not likely that any women so identified would be significantly damaged by these efforts to improve their self-esteem, their skills in living and mothering, and their ability to love their daughters.

There are other studies suggesting useful innovations for improving coping skills in children, for improving mothering, and for improving teaching skills in mothers with borderline intelligence. These are best approached through a preventive trial design.

The preventive trial design is emphasized in this review because it gives the most direct information on both relative and attributable risks of undesirable outcomes. Alertness to opportunities to conduct preventive trials will speed up the acquisition of knowledge regarding prevention.

Preventive trials sometimes require dangerous or anxiety-producing interventions. These preventive trials necessarily represent a late stage in a sequence of epidemiologic studies. But preventive trials which remove a risk or counteract a risk with a harmless or desirable intervention do not need to await the accumulation of supporting data. Such preventive trials can sometimes be the first stage of investigation.

NOTE

1. This refers to the WHO ICD (22) category "senile dementia" (attributed to senile brain disease). It is currently believed that what was formerly referred to as senile brain disease is actually Alzheimer's disease. Paradoxically, Alzheimer described his "pre-senile dementia" as occurring only before age 60. In this study no case of senile dementia before age 60 was observed.

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DISCUSSION

(Dr. Gruenberg made his presentation just before the working group sessions, and the discussion of his paper therefore appears after the paper of Drs. Coursey and Buchsbaum.)

II

THE DEPENDENT VARIABLES: MAJOR MENTAL DISORDERS

In prospective epidemiologic research, the risk factor is taken as the starting or independent variable, and onset or aggravation of the disorder is the outcome or dependent variable. The purview of this conference is defined by four major groups of mental disorders, and we therefore consider the risk factors first in terms of those outcomes.

THE CURRENT STATUS OF RESEARCH WITH CHILDREN AT RISK FOR SCHIZOPHRENIA AND OTHER FORMS OF PSYCHOPATHOLOGY

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INTRODUCTION

This brief report describes some recent findings that suggest proximate and specific risk factors that may have precursor status in the severe mental disorders. The results are derived from projects focused on children presumed to be at risk for schizophrenia and other forms of psychopathology.

These findings are provided in many of the recently completed progress reports of major investigators in the children-at-risk-for-schizophrenia field. The reports became available as the result of a most fortuitous circumstance. On March 11-13, 1980, the Consortium of High Risk Projects, under the direction of Norman Watt of the University of Denver (32), assembled in San Juan, Puerto Rico, to hear reports of progress and activity in the various projects. A detailed volume describing the conference will provide complete reports a year hence.

Progress on risk factors has been made via the study of the development of children who may be predisposed to schizophrenic pathology in later life. Some simple facts suffice: In 1972, when the first major risk research conference was held, the risk studies, with several prominent exceptions, were in their infancy. On a time scale, the oldest was one conducted by Barbara Fish (9,10). Hers had been a long-term followup of a small set of case studies of a highly deviant group of infants born to schizophrenic mothers. The infants, an atypical set when arrayed against the later group of newborns who were to be evaluated in the 1970s, were marked by what Fish termed a "possible neurointegrative defect," as evidenced by erratic and disorganized patterns of response in their activity, alertness, vestibular functioning, autonomic stability, and proprioceptive responsiveness.

In 1972, the oldest broad-gauged systematic risk research effort, begun in 1962, was based in Copenhagen, and presided over by Drs. Sarnoff Mednick and Fini Schulsinger (28). This duo were the true progenitors of the risk projects that burgeoned in the early 1970s in the sense that they had enlarged the research enterprise, removing it from the interesting idiography of the case study and moving it toward a large-N, nomothetic orientation. The design and even some of the methodology were ripe for emulation: large numbers of index and matched control children; a wide-band set of clinical, laboratory, and experimental methods, all projected as potential precursors for schizophrenia and derived from Mednick's earlier theoretical formulations of the possible genesis of schizophrenia.

The expansion of the risk studies here and abroad can be illustrated simplistically by numbers and, in a far more complex manner, by noting the heightening maturity evidenced in the selection of variables, the different types of research designs, and the statistical analyses that have now followed in the wake of earlier studies. First, for the counting measure: From the slim beginnings of the 12 cases reflected in Fish's early studies, I would now estimate that over 1,000 children of schizophrenic parents have undergone study and evaluation and, that more than 500 other psychopathological control children have been similarly seen, approximately 75 percent of whom have been offspring of affectively disordered parents. To these risk groups have been added substantially more than 1,000 normal control children, some of whom have been matched to their index counterparts on various demographic and familial attributes, while others have been randomly selected as subjects.

Numbers, of course, provide only a limited picture of scientific advance. What has been done to and with these children and what has been discovered are far more important.

But a caveat is in order, and it is one that can well constitute a first law of psychopathology research. **The perceived ease of a research area in psychopathology is directly proportional to our lack of knowledge about it.** In the search for developmental antecedents to schizophrenia, our lack of knowledge is striking. So I urge a realization that we are dealing here with a research area that has enjoyed a brief lifespan of a mere 12-15 years. In common with most adolescents, risk research has a great deal to learn, but it has gone about the business of acquiring that needed knowledge with uncommon dedication and vigor.

Nevertheless, we have become increasingly aware of the problems that accompany the developmental study of children at risk. Here is a sampling of such difficulties:

1. The difficult task of selecting variables that will have presumptive power to reflect the risk status of children

2. The need for a solid core of normative developmental data with reference to each variable that extends from childhood into early adulthood, thus permitting judgements to be made about deviations from normality, and the range of variability reflected in normal performance

3. The necessity for comparable studies with active and remitted schizophrenics so as to provide two types of additional knowledge: (a) whether or not the variable in question appears to have a central, a peripheral, or a nonexistent role in mental disorder; and (b) whether it suggests the likelihood of continuity extending from the premorbid period into the phase of active disorder and its remission

4. The difficulty of replicating findings across research programs that may be heightened by: (a) variations in diagnostic criteria across parental cohorts; (b) the presence of demographic, age, sex, and cultural dissimilarities across index samples; (c) variations in familial factors, including intactness and adaptational status of the nonschizophrenic spouse; (d) the presence of a long delay intervening between the measurements of the dependent variable and the determinate diagnostic status of the index child; (e) the overall difficulty of matching the factors above across studies when adjudging the status of the dependent variable as to its centrality, peripherality, or irrelevance when there is a failure to replicate. However, if replication is achieved suggesting that differences are likely to be incidental to the at-risk factors, then the measure can be accorded consideration as a potential precursor variable in any second generation of longitudinal developmental studies of children at risk.

Breakdowns And Casualties

The closing session of the San Juan Conference was a symposium on "Casualties and Competencies Among Samples at Risk." In terms of actual diagnosed schizophrenia in the offspring, the number of cases is relatively small at this time—a factor which invokes caution in discussing risk factors. It is true that some of the index children in the more senior studies are now moving into young adulthood with its accompanying heightened risk for schizophrenia; the average age of the children in the Copenhagen study will be approximately 33 this year. But at the time of the 1972-1973 diagnostic assessments, their average age was 25 and at that point there were 17 high-risk offspring and 1 low-risk offspring who had received a consensus diagnosis of schizophrenia. Seven years later, it is likely that additional offspring will be added to the schizophrenia count, although as the offspring grow older it is possible that some of the first admissions for psychosis may present more of a schizophreniform disorder.

The same 1972 assessment procedure reveals a rather marked degree of other forms of psychiatric disturbance in the high-risk group (18). The tabular presentation in table 1 is adapted from findings reported by H. Schulsinger (28). As derived from the consensus diagnostic totals in the table, the number of "disturbed" offspring is represented by 141 cases or 81 percent of the recorded total number of cases (and 69 percent of the original index group).

The comparable figures for a low-risk control group are 68 percent of the recorded totals in the table (and 60 percent of the original control group). These high proportions deviate from the probability estimate of 50 percent for the high-risk group suggested originally by Mednick and Schulsinger (1968) in their initial descriptive article about the Copenhagen project. However, with selection emphasis on the mother as a severly disordered process-type patient with nonintact family status and with controls matched to index on a range of demographic and familial variables, these high counts of psychopathology may reflect the selection pattern set out by Mednick and Schulsinger at the very beginning of the study.

I can report briefly on several of the maternal characteristics associated with schizophrenic outcome. In 1975, Mednick, Schulsinger, and Schulsinger (19) noted three

characteristics of the schizophrenic mothers which differentiated the schizophrenic from the nonschizophrenic offspring:

1. The mothers of the children who became schizophrenic developed their illness at a younger age;

2. Most of the mothers of schizophrenics were separated from their children when the child was quite young. Many of the children were placed in children's homes; and

3. Mothers of the schizophrenics had more difficulties with the birth of their child.

Table 1. Current diagnostic status of high-risk and low-risk (in parentheses) subjects in the 1972 assessment of the Mednick-Schulsinger project. Adapted from (28).

Diagnosis	Interviewer Rating		"Consensus" Diagnosis	
Schizophrenia	13	(1)	15	(1)
Borderline states (includes schizoid and paranoia)	71	(5)	55	(4)
Psychopathy	5	(4)	5	(4)
Other personality disorders	26	(10)	22	(9)
Neuroses	34	(44)	30	(33)
Nonspecific conditions	0	(0)	13	(11)
No mental disorder	23	(27)	25	(27)
Other conditions (includes affective and paranoid psychoses)	1	(0)	1	(0)
Diagnostic disagreements			7	(2)
TOTALS	173	(91)	173	(91)

In a later analysis, Talovic et al. (29) reported that two of the major maternal differentiators, accounting for 38 percent of the variance related to offspring's breakdown, were:

1. A psychotic episode precipitated in the mother within 6 months of childbirth (which more typically involved a sibling's birth rather than that of the schizophrenic offspring)

2. The mother's history of unstable relationships with men

Of additional interest in the diagnosed schizophrenic group is the significantly younger mean age of the mothers at schizophrenic onset, at their first psychiatric hospitalization, and at the birth of a child.

These findings lead me to a study that I consider to be one of the most creative and significant in the risk field. Rodnick and Goldstein (23), as part of their high-risk UCLA project, have reported on the relationship of maternal premorbid adjustment and the recovery of the "mothering function" in acute schizophrenic women. Their study may provide some much needed data on the relationship between the genetic contribution of the mother's schizophrenia and the experiential contribution of her inadequate care-taking as factors heightening the risk potential in her offspring.

With the closing of many of the mental hospitals in California, acutely ill schizophrenic patients have come to community mental health centers to be cared for and treated briefly and then returned to their homes. What impact does such a radical revision in treatment have on the care-taking function these women can provide for their children over the span of 1 year following a 1- or 2-week-long period of hospitalization? The study group included 8 poor premorbid and 19 good premorbid patients. Their median stay in a crisis-oriented mental health center was 10 days. Upon return to their homes, the patient and husband were seen, and home observations were made with followup at 30 days, 6 months, and 1 year following discharge.

These poor premorbid mothers were, on the average, 7 years younger than the good premorbid mothers (mean age 21 versus 28); their children were also younger (mean for oldest child 1.75 years versus 7.47 years; youngest child .63 years versus 3.47 years).

> Typically, the youngest child of the good premorbid mother at the time of her first psychotic break is in middle childhood, while there is usually a young, recently-born infant in the home of the poor premorbid mother. The latter resembles postpartum psychosis more than does the former (p. 625).

Interviews and home visits enabled the investigators to rate aspects of care-taking in relation to the child, ranging from an extreme of unresponsiveness, apathy, and indifference to the other extreme of warm, affectionate, enthusiastic enjoyment of the child. The data reveal that 6 months were required before the good premorbid mothers could return to a level of adequate care-taking, with 1 year required by the poor premorbid group.

Consider the interaction at work here. A good premorbid mother breaks down in her late twenties; her children are older. They have known good, or at least normal, childcare for a significant timespan. The poor premorbid mother is younger; there is at least one infant at home who for the span of a year will be exposed to inadequate mothering with attendant threats to the attachment process. Inadequate nurturance and

genetic predisposition are likely interactive factors in generating vulnerability in the infant. The linkage to the Copenhagen findings, although inferential, seems evident since poor premorbidity is an attribute of the chronic-process mothers who comprised the Danish sample.

If we examine the findings of other risk groups, we see a very slow but steady accretion of diagnosed schizophrenics and clinically deviant cases among the offspring. At UCLA Goldstein and Rodnick looked at risk from a different vantage point—starting not with schizophrenia in parents but with the disturbed behavioral states in adolescents that bring offspring and parents to a university psychological clinic. Their 5-year followup (24) of a large group of families at intake reveals that two children of the original cohort received a diagnosis of "definite" schizophrenia, while an additional eight or nine cases received (Wender) ratings suggestive of a schizophrenia spectrum disorder. These persons, when appraised by their intake symptoms, came from subgroups that either were marked by active family conflict between adolescent and parents (about which more will be said in the next section) or were brought to the clinic because of their withdrawn, asocial, and isolated behavior.

At the New York State Psychiatric Institute, Erlenmeyer-Kimling's (7,8) risk group has reached an average age of 17.5 years, and a recent assessment reveals that 8 of the total original sample (N = 205) have been hospitalized for psychiatric reasons, while 15 more are or have been in psychiatric treatment. These groups which have been tentatively evaluated diagnostically were quite diverse and have been identified more conservatively under the more general rubric of **clinically deviant.**

Of the 15 subjects in treatment, 8 offspring have 1 schizophrenic parent, 2 have both parents schizophrenic, and 4 have depressed mothers.

The correlates of the 23 clinically deviant subjects, when compared with the other high-risk offspring, psychopathological controls, and normal controls, have been tentatively identified by the research team:

1. There is a tendency for high-risk subjects of lower IQ to be more likely candidates for clinical deviance than their higher IQ counterparts.

2. Human figure drawings are noncontributory; trends of deficit performance on the Bender-Gestalt are seen for hospitalized risk subjects relative to their nondisturbed high risk counterparts.

3. Clinically deviant risk subjects have relatively poor total neurological scores and less adequate performance on motor tasks, but these deficits are not specific to parental or child psychopathology.

4. Sustained attention, as measured by the Continuous Performance Test (CPT) and Attention Span test, is most deficient in the clinically deviant offspring who are at risk for schizophrenia.

5. Recovery time of the electrodermal response does not differentiate between clinical deviance as opposed to nondeviant behavior in the risk groups, suggesting "a lack of robustness in the relationship between risk for schizophrenia and the electrodermal pattern found in the Copenhagen project."

Caution is required when interpreting these preliminary results about casualties and discriminators among the high-risk offspring. The groups are young and, when hospitalized, are typically first admissions. In the future, others may develop serious and persistent disorders, while some persons seemingly disabled now may recover and leave their "sick" status behind. A decade hence, more stable indications of psychopathology in the high-risk subjects are likely to be found, and subsequent reappraisals may provide evidence of more stable relationships between predictors and outcomes.

In the section that follows, brief descriptions are given of some of the highlights of recent results obtained in the various high-risk programs of research. Although it is an injustice to try to telescope the contents of multiple projects into a few spare sentences, in this final section I summarize my view of the status of specific variables as reflected in the data accounts provided by various investigative groups.

RESEARCH FINDINGS ON SPECIFIC RISK VARIABLES

The Pregnancy Phase: Prenatal Assessments Of Mothers

Of particular interest in the area of pregnancy and birth data is the risk project which began in 1973 under the joint direction of Thomas McNeil and Lennart Kaij of the University of Lund in Malmö, Sweden (14,15).

Over a span of 4 1/2 years at 11 different hospitals in 11 different cities co-principal investigator McNeil was present, with parental permission, as an observer at the birth of 83 percent of the samples before partus or within 2 hours post-partum. Thus, in the near future, this project will be able to provide the risk field with carefully detailed data on the birth and immediate post-partum status of infants and mothers. At this point, final data reports are being prepared. However, McNeil and Kaij suggest that a variety of stressful circumstances surround pregnancy. When compared with controls, index cases reported "significantly . . . less interpersonal support" for the pregnancy, poorer relations with husbands and parents who were more often negative to the pregnancy. The mothers too more frequently reported negative attributes to the pregnancy. There was a significantly greater number who reported being "panicked" or "very worried" as to the possible malformation of the baby and having greater concern about their own mental health. Index cases on interview showed a greater trend toward more serious mental symptoms.

However, these are nondifferentiating characteristics which apply to a variety of disordered index cases. Sameroff's data (27) would suggest that poverty has equivalent power for eliciting similar correlates.

Therefore, the above factors are unlikely to be powerful discriminating risk variables solely for schizophrenia.

Pregnancy And Birth Complications

First elaborated by Fish and Mednick/Schulsinger, this variable seems to possess considerable specific power for schizophrenia. An excellent analysis of a large body of literature on obstetric factors deserves summary:

> While the extensive literature on etiologic factors in schizophrenia . . . suggests that obstetric complications are definitely not the sole answer to the etiology of schizophrenia, the extensive literature . . . and . . . new results also suggest that obstetric complications are a risk-increasing factor to be taken seriously in the etiology of schizophrenia. The most important tasks remaining would seem to be to investigate in what ways such complications affect the developing individual, in what way they relate to other premorbid characteristics of schizophrenics, and in what way they interact with or complement other etiologic factors in the development of schizophrenia (14, p. 426).

Neonatal Neurological Assessment

Data from several projects suggest that a **subset** of infants born to schizophrenic mothers show neurological deviations, but the proportion who do so is relatively small and likely evident in other forms of psychopathology, although more significantly so in schizophrenia. In the Lund study, only the Schizophrenia Index group showed a suggestively higher rate in the category "suspicious but not certain deviation." "Clear abnormalities" are typically infrequent in index cases, and a small number are to be found among control subjects. Fish's cases of a severe "neurointegrative defect" are atypical of index infants, but the report that a small subset show neurological abnormalities has been confirmed in other studies including a study conducted in Israel, as described by Marcus et al. (13).

Post-Partum Mental Disturbance

This seems to be an increasingly important variable worthy of pursuit. In the Lund study, 56 percent of the total index groups were either "psychiatrically hospitalized or in contact with a psychiatric unit" during a period up to 6 months after birth. The Copenhagen study affirms the power of this factor in accounting for a large portion of the variance involved in offsprings' subsequently diagnosed mental disorder. Severity of maternal disturbance also appears to be a significant factor.

This is a variable that deserves careful attention across risk studies.

Adoption And Foster Placement

A potentially important indicator of the mother's social incompetence and severe anxiety in the last months of pregnancy is the factor of adoption or foster placement of the infant. Sameroff and his colleagues report that the condition of the infants was worse in the placement group. Their mothers had significantly more illnesses during pregnancy, their infants had more problems after birth, and the infants differed significantly in birth weight. Not one of the six placements in Sameroff's project was over 2,800 grams at birth, while four of the six spent the newborn period in the special care nursery (25,26,27).

Mednick and Schulsinger have from the beginning of their project identified this factor as a powerful differentiator not only between Index and Control offspring but between breakdown Index and nonbreakdown Index cases.

Therefore, this appears to be a significant variable in an important but not a random subset of schizophrenic mothers.

Offspring Temperament

Data, although preliminary, suggest that obtained differences are generally small and nonsignificant. Chronicity across different types of maternal psychopathology is reflected in Sameroff's project in "more active, irregular, withdrawn, intense, and negative mood, with lower levels of adaptability, and threshold to stimulation."

Cognitive Functioning

To a large extent, intellectual test performance may be somewhat depressed but not significantly so. Chronicity rather than type of psychopathology is likely involved.

Attentional Functioning

This is one of the most significant differentiators which has been affirmed across different projects. Sustained attention, particularly under conditions of distraction or degrading of the targeted stimulus, generates deficit performance in subsets of children born to schizophrenic parents. Signal detection analysis reveals the deficit to be related to **d'**, a measure of signal/noise discrimination or sensitivity (3,5,6,20,21). In one study, hyperactive children who are also deficient attenders have been shown to reveal β deficits—a measure of response caution in signal detection theory (20). Of considerable importance is the finding by Cornblatt and Erlenmeyer-Kimling (3) that attentional deficits based on earlier appraisals of the risk children are related to deviant behavior as the children grow older. This provides support for the predictive power of attentional dysfunction with regard to later psychopathology.

Tests of Information Overload, Memory Lag, Span of Apprehension in varying degrees and across projects reflect the presence of attentional deficit in "outlier" subsets of index children. This variable is worthy of continued and extended investigation.

Psychophysiological Functioning

Reconciliation of disparate findings remains a necessity given the discrepancy in findings reported by several investigative groups.

In table 2 the electrodermal findings of the Mednick-Schulsinger and Erlenmeyer-Kimling studies are briefly summarized.

At the Rochester Conference, Mednick (16) presented evidence that the discrepancies could be resolved by a careful examination of the attributes of different samples of children and their parents who had been tested. One factor would be "the type or grade of schizophrenia" (p. 443) of the affected parent; another would be the sex and the

age of the children undergoing autonomic appraisal (postpubertal boys are more labile than postpubertal girls); still another would be the symptom pattern evidenced by the diagnosed schizophrenic patient (hallucinations and delusional manifestations correlate highly with fast skin-conductance recovery). At the family level, Mednick urged that attention be given to the intactness-nonintactness factor. His high-risk offspring group had been selected to insure severe process schizophrenia in the hospitalized mothers, as a result of which three-quarters of the Danish families were nonintact. On the other hand, the New York State Psychiatric group had been selected for family intactness. In reanalyzing the Danish data, Mednick demonstrated the noncomparability of the two data sets. Finally, again with regard to the family, Mednick cites as an important factor the curious assortative mating of biological fathers with the Danish schizophrenic mothers; 49.6 percent of them were known to the Danish police, of whom 40.6 percent had had at least one conviction. The interpretative potential of specific family differences across studies provided by such a marital combination lies in Mednick's report that sociopathic individuals show skin-conductance hyporesponsivity, thus attenuating (probably on a genetic basis) the offspring's psychophysiological responsiveness. Thus, criminality in the spouse, Mednick argues, can modify the autonomic responsiveness and speed in the rate of recovery of high risk-offspring born to the mother who has been diagnosed a schizophrenic.

Table 2. Electrodermal findings. UCS refers to "unconditioned stimulus." Adapted from (8).

Mednick & Schulsinger	Erlenmeyer-Kimling et al. Sample A
(1) High-risk subjects had shorter latencies to the UCS.	(1) High-risk subjects had longer response latencies to the UCS.
(2) High-risk subjects had greater amplitude of response than controls.	(2) High-risk subjects had the same amplitude of response as controls.
(3) High-risk subjects had shorter recovery times than controls.	(3) High-risk subjects had longer recovery times than controls.
(4) High-risk subjects failed to habituate to UCS over the course of testing but controls habituated.	(4) All subjects habituated to USC over the course of testing.

In the most recent analysis of their results, Erlenmeyer-Kimling et al. (8) have examined the severity-of-schizophrenia factor in the affected parent on the assumption that, at a genetic level, a relationship between family intactness and the autonomic nervous system variable must implicate the severity factor. Initial reports indicate a negative correlation between the mothers' global assessment score (which serves as a measure of severity of functional impairment) and autonomic recovery of $r = -0.23$ "indicating that the children with the **least** severely-ill mothers (high GAS scores) tended

to have faster recovery than children of more severely-ill mothers." The research group adds:

> Thus, in our "intact" families, there is no indication that recovery is associated with a more genetically meaningful variable, severity of mother's illness, in a way that would be expected if recovery is relevant to the prediction of risk for schizophrenia (p.28).

In addition, a review of the data on 23 offspring who are now showing clinical deviance (8 hospitalized; 15 in psychiatric treatment) fails to reveal statistically significant trends toward faster recovery when compared with the remaining high-risk or normal-control subjects.

At the San Juan Conference, Prentky, Salzman, and Klein (22) presented the results of a study of "Habituation and Conditioning of Skin Conductance Responses in Children at Risk." These subjects consisted of 42 7-year-old male children and 57 10-year-old male children obtained from a subsample of families participating in the University of Rochester Child and Family Study. Index-parent diagnoses based on DSM-III criteria were used to produce three groups of parents: (1) all subgroups of schizophrenia and schizoaffective disorder; (2) affective psychosis (bipolar affective disorder—manic, depressed, or cyclic; and unipolar depressive disorder—psychotic or severe); (3) nonpsychotic index parents, including personality disorders, anxiety disorders, situational reactions, and mild or moderate nonpsychotic depressive reactions.

The results of this study indicate that greater conditioning occurred in the 10-year-old offspring of schizophrenic parents but not in the 7-year-old group; there was no systematic evidence of greater responsiveness to intense stimuli, nor was there evidence of more rapid skin-conductance recovery. In both age groups the high-risk subjects evinced the longest recovery times.

There is something of a paradox in these discrepant findings. Are there developmental trends in electrodermal activity? Mednick's group and Erlenmeyer-Kimling's groups are older. If, as Venables et al. (cited in reference 18) have suggested on the basis of cross-sectional data obtained with a different cultural group, conductance levels begin to rise from age 15 into adulthood, this could be one possible explanation for the discrepancies.

Continued pursuit of the psychophysiological status of "outlier" groups of index children, particularly those whose risk status is actualized into formal mental disorder, appears to be an important research area for future study.

FAMILY INTERACTION STUDIES

There are two major projects directly concerned with intensive observational studies of family interaction and the molecular analysis of these interactions. The UCLA project (Rodnick-Goldstein) has been following up the behavioral outcomes of those adolescents who participated in their clinic study of disturbed adolescents and their families. The University of Rochester program (Wynne et al.) has a wide-ranging set of studies that include taped protocols of parent-child free play interaction, consensus Rorschach, task conflict resolution, etc.

The UCLA project includes a subset of studies in which parental affective styles of communication have been measured on the basis of direct family discussions and communication deviance (CD) measures derived from individual TAT protocols obtained from the families of the disturbed, nonpsychotic adolescent group. A combination of the two measures related best to outcome at 5-year followup in which 52 of the original 65 families participated. Those adolescents whose parents revealed a pathological affective style of communication and showed high levels of communication deviance developed schizophrenia spectrum disorders when they reached young adulthood.

The intriguing aspect of this finding is the overlap of the assessed affective style with the expressed emotionality (EE) component developed by Brown, Wing, Birley, Vaughn, and Leff at the Maudsley (e.g., 1,30,31). **Support, Criticism, Guilt, Induction, Intrusiveness** (both critical and neutral in tone) constituted the EE category system. The Wynne-Singer CD measure was used to score TAT protocols (12).

At followup, RDC criteria and Gunderson's Borderline Evaluation Schedule, based on interview data, were used to assess the subjects' diagnostic status and to assign ratings based on the Wender scale ranging from normality to definite schizophrenia.

When the two measures were combined, all of the eight individuals whose parents manifested high CD and also revealed a negative affective style received diagnoses within the schizophrenia spectrum. Nine other individuals at the other end of the spectrum who were rated essentially as free of serious psychopathology had parents whose task performance was essentially free of CD and who had a positive affective style (4).

More recent research has focused on an analysis of the early family interactions that were part of the original family-assessment procedures. Here, analysis reveals that it is the high CD parent who takes the central role in family discussions and is likely to dominate the family. In father-centered families, low CD groups were marked by clear communication and affect sharing; high CD groups by rigidity and avoidance of affect sharing (24).

Reports from Rochester based on family interactions in free play and the consensus Rorschach procedure enable a delineation of presence or absence of active/warm interactions. Schizophrenic families are markedly deficient in providing such a positive affective climate when engaging in such interactional procedures (2,11).

Although there are far more detailed analyses in progress, it would appear that continued exploration of these important interactional studies would be desirable.

At the Conference, other aspects of social functioning of the high-risk offspring were presented, and these, too, will require the analysis of "outlier" subsets of children at risk who provide early signs of social maladaptation and peer rebuff.

These observations represent a brief summary of only a portion of the research papers and the various projects presented at the San Juan Conference. A forthcoming volume will undo the neglect imposed here by editorial constraints.

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DISCUSSION

Dr. Klerman: Would you comment on the two criteria for risk factors given by Dr. Regier and Dr. Pardes, namely, that risk research may be useful either in the design of field studies of an epidemiologic nature or in possible preventive intervention.

Do you think these studies of high-risk children have progressed far enough so that you can identify variables or factors that are ready to be put into large-scale community field studies of an epidemiologic nature or perhaps lend themselves to preventive intervention, even on a demonstration basis, for schizophrenia?

Dr. Garmezy: The question is an excellent one, and my reply will not be a very satisfactory one. First, it will be a reply that simply represents my personal opinion. I am aware that many of my colleagues in the risk field would not agree with what I am going to say and quite likely would have a more positive response.

My answer is that I don't think it would yet be possible to identify variables that are ready for large-scale community field studies. Nor am I persuaded that we know enough about children at risk for schizophrenia to form the basis for prevention programs, even if they are only intended as pilot demonstration programs.

Having said that, I feel it necessary to go on and add that my view would not only hold for children-at-risk studies but for many of the other areas of research in schizophrenia, including variables drawn from biochemistry, pharmacology, neurophysiology, genetics, sociology, and anthropology. And yet, I do believe that we stand on the threshold of discoveries about schizophrenia from a biogenetic perspective and, less so, from a developmental perspective.

In the field of risk research which is largely, but not entirely, a literature of cross-sectional and longitudinal research with children of schizophrenic mothers, there are indications that the domain of attention and information processing may have future payoff. Some of the psychophysiological studies may suggest some promise, too.

But, even if I had more confidence in the predictive power of the results of these studies in terms of ultimate outcomes, I question whether the laboratory methods that have been used in these studies can be readily incorporated into field studies designed to provide sound epidemiologic data about schizophrenia.

At this very moment the recent appearance of DSM-III requires of risk investigators a reappraisal of their diagnostic assignments for previously or currently psychotic parents. Their status defined the risk quality of their offspring, who were the index children of the many studies I touched on briefly in my report, as well as in earlier published papers.

With regard to the second portion of Dr. Klerman's question, we do not have available a solid core of intervention studies with children presumed to be predisposed to the disorder. The largest scale study available for appraisal is the Mauritius study. There, Drs. Mednick, Schulsinger, Venables, and their colleagues have selected children on the basis of deviant psychophysiological functioning and exposed a portion of them to the positive intervention of an extended nursery school experience (3 years) that provided not only opportunities for social peer interaction but also nurturant care from adults, training in social skills, and wholesome nutrition. Children in a control group selected on the basis of similar psychophysiological status have not received this positive environmental intervention.

My hesitation in viewing this large-scale venture as a test of the efficacy of intervention is a compound of many questions: Are the selection criteria revelatory of risk for schizophrenia? Are the basic developmental data in place with regard to the psychophysiology of children of preschool years and beyond? (Such data are now being

collected by Venables, but on a cross-sectional rather than a longitudinal basis). Can we be confident of the transposition of the risk findings, without regard to the issue of replicability, from one culture to another?

If all these questions had satisfactory answers at this point, that would constitute a very solid beginning. Beyond would be the decades-long wait for the emergence of schizophrenia in a subset of the Mauritius children, without a high degree of confidence that it would be possible to delineate the roles played by selection variables or intervention modalities in positive or negative outcomes.

This study and others may indeed prove to be worthy in terms of their design and procedures, meticulousness of execution, and ultimate findings and yet not speak to the very critical question raised by Dr. Klerman.

In terms of reducing risk, there are some things that obviously one would want to see done. One would be good prenatal and postnatal care for mothers who have known severe mental disorder. But we do not think of such interventions as specific to the prevention of schizophrenia but rather aimed at fostering the physical and mental health of all children. What one tries to do is reduce the deprivational status of children; risk studies, such as those of Sameroff and Zax, indicate that poverty in mothers heightens risk in their children.

Dr. Erlenmeyer-Kimling: It may be useful to give some more details from our study. We have been following 80 children of schizophrenic parents since 1971, as well as 25 whose parents had affective disorders and 100 whose parents were normal. The median age is now about 17 1/2. Five of the 80 high-risk subjects have been hospitalized, compared with 2 of the 25 children of parents with affective disorders and 1 of the 100 children of normal parents. Another 15 subjects are in treatment for serious problems, distributed among the three groups in nearly the same proportions.

We have been especially interested in examining the results of the tests administered back in 1971-72 to see whether there was anything that might have distinguished these subjects who are now clinically deviant from other subjects who are not showing psychopathology in late adolescence. The findings emerging about the original test results for the 5 hospitalized and 10 treated children of schizophrenic parents are showing some consistency, while there is no consistent pattern of results for the clinically deviant children in the two comparison groups. The 15 clinically deviant high-risk subjects had a mean IQ that was 11 points below that of the total group at high risk for schizophrenia, with a large relative deficit in verbal IQ. These subjects also performed poorly on the Bender-Gestalt test and showed deficiencies on the Lincoln-Oseretsky test of motor impairment and the neurological examination. All but 3 of the 15 were below the 5th percentile of the normal comparison group on the Continuous Performance Test and had poor scores on the Attention Span test. Application of analyses based on signal detection theory to the attentional data suggests that the clinically deviant high-risk subjects had unusually poor ability to discriminate among stimuli, compared to other subjects in the high-risk group or in the two comparison groups.

An important point, however, is that no one of the variables, alone, could have been used to predict the later distribution of psychiatric problems in this group of children at high risk for schizophrenia. The composite picture seems to be necessary.

BIOLOGICAL RISK FACTORS IN SCHIZOPHRENIA

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To characterize the syndrome of schizophrenia, we should begin with Bleuler who first named it and with Kraepelin whose "dementia praecox" was the basis of Bleuler's syndrome. Both agreed on the fundamental characteristics: "The disease is characterized by a specific type of alteration of thinking, feeling, and relation to the external world which appears nowhere else in this particular fashion (1)"; "...the weakening of judgement, of mental activity and of creative ability, the dulling of emotional interest and the loss of energy, lastly, the loosening of the inner unity of the psychic life would have to be reckoned among the fundamental disorders of dementia praecox, while all the remaining morbid symptoms, especially hallucinations and delusions...would be regarded more as secondary accompanying phenomena...the former constitute the real characteristic of the clinical state and can be demonstrated in each individual case more or less distinctly; the latter may be present but may also be absent...(17)." In addition to these features, both pointed out the importance of a clear sensorium, the chronicity, and failure to return to the previous level of mental integrity.

The limits of Kraepelin's syndrome were extended by Bleuler. Although each of them recognized a subgroup of "simple schizophrenia" characterized by the fundamental symptoms but without the secondary and accessory ones, Bleuler introduced the term "latent schizophrenia" which he did not completely define: "In this form, we can see **in nuce** all the symptoms and combinations of symptoms which are present in the manifest types of the disease (1)." Kraepelin later agreed but felt that Bleuler was defining it too broadly.

Both authors described an insidious onset in young adults as typical, although they recognized that the essentially chronic syndrome could sometimes have an acute onset. They would not, however, have included "good-prognosis schizophrenia" which is characterized by acute onset, brief duration, and complete remission. For that reason, "schizophreniform psychosis" was used to describe that syndrome by European psychiatrists. In 1959, however, Schneider (28) undertook to revise radically the

symptoms characteristic of schizophrenia by disregarding the features which Kraepelin and Bleuler had regarded as fundamental—impoverished affect, ambivalence, autism, thought disorder, chronic course, insidious onset, incomplete remission—and relying instead on any one of several "first-rank symptoms," all of which were particular types of hallucinations or delusions. Bleuler had described such symptoms as " ...partial phenomena of the most varied diseases. Their presence is often helpful in making the diagnosis of a psychosis, but not in diagnosing the presence of schizophrenia." Because these symptoms are dramatic and unusual, they can be elicited easily and with considerable reliability, but their validity as sufficient, discriminating, and useful criteria for schizophrenia has not been established. The widespread acceptance of these meager criteria for schizophrenia, which would not have been accepted by Kraepelin and Bleuler, has served to befuddle the diagnosis and treatment of schizophrenia as well as the research on it.

HETEROGENEITY OF SCHIZOPHRENIA

Although Kraepelin and Bleuler recognized in the various forms of schizophrenia certain common clinical features and assumed them to be the result of a common "morbid process," both recognized etiological diversity in the syndrome, Bleuler going so far as to entitle his monograph "The Group of Schizophrenias." Nor is there any reason today to think of schizophrenia as a unitary disease, and a substantial number of observations argue against that concept (18).

The various clinical subtypes—simple, paranoid, catatonic, hebephrenic—suggest different morbid processes in addition to one which may be common to all. There is also considerable variation in such clinical features as dementia, amount and quality of affective disturbance, onset, course, and outcome. The occurrence of schizophrenia in various relatives of schizophrenics does not fit a simple Mendelian model, and studies of kinships of such patients yield families with dominant patterns, recessive patterns, or no family history at all.

In addition, a substantial number of diagnostic procedures and biochemical tests are positive in some schizophrenic patients, but there are none thus far that are positive in all. These include neurological manifestations, electroencephalographic findings, abnormalities on CT scan or on eye-tracking, monoamine oxidase activity in platelets, and many other biochemical findings. All of these discrepancies are readily accounted for by etiological or pathological heterogeneity.

PROGNOSTIC MARKERS

To the extent that any abnormality which is found antedates the clinical manifestations or faithfully accompanies them, it may serve as a useful prognostic or diagnostic sign in at least the subgroup of patients to which it applies. Furthermore, if the incidence of the finding approximates the empirical risk for schizophrenia in different populations (i.e., in 40-50 percent of MZ twins of offspring of dual matings, 10-15 percent in siblings of schizophrenics, and 1 percent in the general population), the possibility is enhanced that such a finding could be a useful predictor of later morbidity.

GENETIC RISK

Evidence for the existence of substantial genetic risk and its estimation has come from studies of families and twins of schizophrenics (6) and from genetically related individuals separated from each other by adoption (8,12,27). Each strategy has certain limitations. Incomplete ascertainment tends to inflate the estimates of genetic risk as long as there are more schizophrenics in a population than thos known to psychiatric facilities, since a family or twinship with more than one schizophrenic has a greater likelihood of being discovered. The reliance of psychiatric diagnosis on subjective evaluation would tend to favor the diagnosis of schizophrenia in relatives of schizophrenics, unless that diagnosis is made without such knowledge. To the extent that environmental factors are shared by members of a family or by MZ twins, they may also augment the variance attributed to genetic factors.

Studies of adopted individuals and their relatives can minimize some of these biaes but are not completely free of the possibility for error. Selective placement of adoptees could augment the risk attributed to genetic factors, while abortion and restraints on adoption of the offspring of a schizophrenic parent artificially diminish the estimates of genetic risk. In the national sample of adoptees in Denmark, selective placement based on socioeconomic status of the fathers is quite low ($r < 0.20$), but removal of the offspring of overt schizophrenics from the sample through the liberal policy of abortion, or restraints on placing such children for adoption, diminishes the incidence of schizophrenia in certain populations. Appropriate controls can obviate the effect of differences between biological and adoptive parents in respect of age, social class, and prevalence of psychopathology, while special strategiese are required to minimize the environmental influences the biological mother shares with the fetus or newborn.

The significantly high prevalence of schizophrenia (and a spectrum of qualitatively similar but less severe syndromes that would be embraced by Bleuler's concept of latent schizophrenia) in the biological relatives of schizophrenic adoptees is indicative of an appreciable genetic risk in a major segment of schizophrenic disorders. This prevalence in biological relatives of schizophrenic adoptees does not significantly differ from values obtained for relatives reared together, indicating that the repeatedly documented familial tendency of schizophrenic disorders is an expression of genetic factors.

The finding by several raters, blind to the relationship among subjects, of a milder type of syndrome (defined variously as latent, borderline, or uncertain schizophrenia or as schizotypal personality) in the biological relatives of adoptees with classical schizophrenia (14) confirms Bleuler's assumption of a latent form of the syndrome and does so in the absence of subjective bias. A similar result was obtained by Essen-Möller and by several other raters in blind diagnoses on MZ twins (6). What remains to be done in the case of both the adoption and twin studies is a further characterization of these milder syndromes genetically related to classical schizophrenia.

It is possible to calculate a more precise estimate of "recurrence risk" of schizophrenia for a particular member of a specified kinship (24) which depends, however, on the assumption of one or another mode of genetic transmission. At the present time, no single mode is consistent with all the empirical frequencies; various models—monogenic autosomal, both dominant and recessive, and polygenic—have been suggested, and none can be ruled out. This is not unexpected where there is etiological heterogeneity. It is interesting (but perhaps simplistic) that, if one deduces from the results in MZ twins that 50 percent of schizophrenics are phenocopies and treats the approximately 50 percent of schizophrenic adoptees without known schizophrenia in their biological relatives as

phenocopies, the remaining pedigrees are quite consistent with a monogenic autosomal dominant type of transmission. A valid genetic marker for one or more homogeneous segments of the syndrome would be of great value in arriving at better defined modes of transmission for subtypes of the broad syndrome which has thus far been defined only in terms of clinical manifestations.

CONTRIBUTIONS OF THE PHYSICAL ENVIRONMENT TO RISK

Although there has been a tendency to equate environmental influences in schizophrenia with psychosocial factors, permitting the development of hypotheses and observations compatible with them, there are many influences in the environment which may operate through biological processes in the etiology or pathogenesis of schizophrenia. Several of these are discussed below.

OBSTETRICAL COMPLICATIONS

A recent comprehensive review of research on obstetrical complications (OCs) and schizophrenia by McNeil and Kaij (20) concluded that present evidence is most consistent with the hypotheses that OCs increase the risk for all types of schizophrenia, that OCs interact with genetic influences on schizophrenia, and that OCs antecedent to the development of schizophrenia are independent stressors, rather than the effects of genes, for schizophrenia.

However, it was noted that the existing evidence is only suggestive, since most studies on OCs and schizophrenia have examined samples of childhood schizophrenics or offspring of schizophrenic parents rather than adult schizophrenics. There is a particular need for more research on sequellae of OCs in adult schizophrenics and controls because most existing studies of OCs in adult schizophrenics have methodological flaws, such as reliance on retrospective reports of birth history.

Jacobsen and Kinney (10) were able to avoid some of these methodological problems in a recent study by using OC data from midwife reports on the births of adult schizophrenics and controls in the Danish national sample of adoptees (13). These midwife reports offered several significant methodological advantages over most previous studies on obstetrical complications and schizophrenia. First, the study of adoptees avoids the confounding of the peri- and postnatal environments which has been a problem in many previous studies. Second, the obstetrical data have the advantage of being based on observations recorded near the time of birth, thereby avoiding the potential inaccuracy and bias of retrospective reports by patients or their relatives. Third, the midwife reports provide a remarkably uniform source of information because midwives attend nearly all births in Denmark and have done so for the last several decades. Moreover, the forms used in reporting and the quality of reporting have remained very similar over the period covered in the study.

In preliminary analyses, total obstetrical complication scores and the incidence of particular complications were compared in the 65 pairs of schizophrenics and controls matched for age, sex, and social class of rearing parents, and born or placed for adoption in the Copenhagen area. They included two subsamples of respectively (1) 34 matched pairs of adoptees and (2) 31 matched pairs of nonadoptees. Midwife reports were

obtained for over 97 percent of these cases. Pregnancy and birth complications recorded in the midwife reports were scored according to a system, devised by Professor Fritz Fuchs, which assigns weights to different complications on a 4-point scale, according to their severity. Using this system, three scores suggested by Fuchs were calculated: (1) a Total score representing the sum of all complications, each complication being weighted by its respective severity; (2) a Frequency score, representing the total number of complications, regardless of severity; and (3) a Severity score, representing the value of the most severe single complication present, as scored in accord with the scale of Fuchs.

Mean complication scores were significantly higher for schizophrenics than controls, using each of the Fuchs' scores, with $p < .05$ for the Total and Frequency scores and $p < .01$ for the Severity score (all p-values two-tailed, using Mann-Whitney U-Test). Schizophrenics and controls were also compared on the individual complications listed on the midwife reports. The complication that showed the greatest difference between groups was prolonged labor, which was significantly more common in schizophrenics than controls (table 1).

Table 1: Prolonged labor in midwife records of schizophrenics and matched controls.

	Schizophrenics	Controls
Present	25	8
Absent	38	56
TOTAL	63	64

$p = 0.0008$, two-tailed value based on Fisher's exact probability test. (Prolonged labor defined as 24 hours or longer for first-borns, 16 or more hours for later born infants.)

A similar pattern of greater mean complication scores in schizophrenics than matched controls was found for the subsample of adoptees, as well as for the nonadoptee subsample, though significance levels were less striking with the reduction of sample sizes in the subsamples. On the whole, the results support the hypothesis that birth complications may be among the causal contributors to schizophrenia, for the results are difficult to explain in terms of biased or retrospective reporting. The higher mean complication score found for schizophrenic than for control **adoptees** argues against an association between poor prenatal and postnatal environments (with the latter being the actual causal contributor to schizophrenia). Moreover, because differences were also found in the nonadoptive sample, where the schizophrenics and controls had been matched for social class of the biological parents, it is unlikely that lower socioeconomic status in the parents of schizophrenics can explain the association.

It is interesting that the specific complication that showed the strongest difference between schizophrenics and controls in this study was long labor. Long labor is one of the birth complications that McNeil and Kaij included as part of an oxygen-deprivation score that was higher in schizophrenics than controls in their data. These results thus suggest that anoxia-induced brain damage may be an etiological factor in schizophrenia, in accord with an hypothesis based on a study of a high-risk sample of children of schizophrenic mothers (21). It is possible that OCs, such as long labor, are associated with schizophrenia because both are effects of other factors, such as the characteristics of the biological parents. However, this explanation could not account for the higher incidence of birth complications in the schizophrenic as opposed to the healthy co-twins of MZ twin pairs discordant for schizophrenia (20, 26).

In summary, several lines of evidence suggest that OCs may play an important etiological role in schizophrenia; further research is needed to clarify that role. A more indirect line of evidence for the importance of perinatal brain injury for the development of schizophrenia comes from research on season of birth and schizophrenia.

SEASON OF BIRTH

One of the more interesting clues to the etiology of schizophrenia is the repeated finding that a higher percentage of schizophrenics are born during the winter or spring months than is true for the general population. Although the winter-spring excess is generally only moderate in size, being on the order of 5-15 percent, it is highly significant in large samples, and its consistency and generality are impressive. An excess of schizophrenic births in the winter or spring has been found in over 20 studies spanning four decades, in samples from the United States, as well as Canada, England, Holland, Germany, Sweden, Norway, Denmark, and, more recently, from Japan, the Phillipines, South Africa, and Australia (3). The winter-spring excess among schizophrenic births has been confirmed by several recent studies using more rigorous methods, including samples of schizophrenics that are very large and representative of an entire State or country, with control groups carefully matched for area and decade of birth.

Several aspects of the available data suggest that the deviant birth pattern for schizophrenics reflects some factor that varies with the seasons rather than the calendar year, and that the factor is probably biological rather than social in nature. The disproportionately high number of schizophrenic births in the winter and spring months holds true in a variety of countries with marked cultural differences, and with different season-of-birth distributions in the general population. Thus, in the United States, births in the general population tend to peak in the later summer and early fall, whereas in Sweden births tend to peak in the late winter and early spring, but the **relative** excess of schizophrenic births remains concentrated in the winter and spring months in both countries.

More strikingly, in samples from Australia and South Africa, the excess of schizophrenic over control births is shifted by about 6 months, corresponding with the colder, winter months in the Southern hemisphere. Finally, the magnitude of the season-of-birth effect is generally greater in schizophrenic samples from areas showing the greatest seasonal variation in climatic conditions. Thus, in the United States, the excess of winter-spring schizophrenic births is greater in New England and the Midwest than in the South. So too, the excess is more pronounced in Northern European countries, with marked seasonal variation in climate, than in Southern Australia and South Africa where

the climate is milder. The apparent exception to this general trend is the large winter excess of schizophrenic births in a sample from the Phillipines, which lies near the equator and shows relatively small seasonal variations in temperature.

Kinney and Jacobsen (15), using data from the Danish sample of schizophrenic and control adoptees and their relatives (12), found evidence consistent with the hypothesis that a seasonally related perinatal brain-injury factor may contribute to schizophrenia, particularly among individuals likely to have a low genetic liability for the disorder. Of particular interest was the finding that schizophrenics judged to be at low genetic risk differed significantly in season of birth not only from those with higher risk and from controls but also from their respective nonschizophrenic biological sibs and half-sibs.

If a seasonally variable schizophrenogenic factor does in fact exist, what might it be? Two general classes of candidates seem particularly promising at the moment. The first class consists of infectious diseases, perhaps involving some kind of slow or latent virus acquired during the pre- or perinatal period. Viral infections are known to show seasonal variations in their incidence and have been demonstrated in the etiology of an increasing number of chronic degenerative diseases of the central nervous system in man as well as other mammals.

A second hypothesis of particular interest is that there may be seasonal variation in newborn hemorrhagic tendency contributing to perinatal brain damage. Seasonal differences in factors such as the quality and availability of agricultural produce tend to result in seasonal differences in body levels of essential nutrients, such as vitamins C and K, which are known to play critical roles in determining capillary strength and blood coagulation properties. These factors in turn help to explain deviant seasonal distributions which have been found for stillbirths and for hemorrhagic disorders in the newborn, which in some European studies show an excess in the late winter and early spring and a lack of a September peak. The winter-spring excess and the absence of a September peak are both hallmarks of the schizophrenic season-of-birth pattern.

In summary, available data are generally compatible with the hypothesis that the abnormal seasonal distribution of schizophrenic births is caused by a seasonally variable environmental factor acting during the pre- or perinatal period. More intensive research seems warranted, particularly on seasonal variation in perinatal viral infections or obstetrical complications such as neonatal hemorrhaging, that may distinguish schizophrenics and controls.

PRENATAL STRESS

Several lines of evidence suggest various types of prenatal stress as perinatal contributors to schizophrenia. Experimental work with laboratory animals has shown that emotional stress induced in the mother during pregnancy can have significant effects on the brain and behavior of the offspring—even after the offspring have reached maturity. The effects of stress on offspring have been found to depend on a number of variables, including the nature and severity of the stress, the time during gestation when it occurs, and the genotype of the mother and fetus who are exposed to stress (11). Other studies have found that human mothers who have experienced stressful events during pregnancy are more likely to have children with behavioral problems after birth (29).

Two studies are of particular relevance to the role of maternal stress in schizophrenia. B. Mednick (22) studied a sample of offspring at high risk by virtue of having a schizophrenic mother, finding that the high-risk children in this sample who had suffered "severe mental breakdown" were significantly more likely than those who had not to have been born of mothers who experienced pregnancy stress. The high-risk offspring who had broken down were much more likely to have had a biological mother whose own mental illness began before or within a year after the child's birth or to have experienced other very stressful life events during her pregnancy with that child. One difficulty in interpreting these results, however, is the possibility that high-risk offspring exposed to greater prenatal stress may also have been exposed to more stressful postnatal environments. They may also have received a greater genetic liability for schizophrenia from their mothers who showed an earlier onset of their mental illness.

Huttunen and Niskanen (9) were able to avoid some of these problems of interpretation by studying the relation between maternal stress and offspring schizophrenia in a sample in which the maternal stress was likely to be independent of the maternal psychiatric status. Using a Finnish population register, they carried out an epidemiological study in which an index group was identified, consisting of 167 persons born between 1925 and 1957 whose fathers died while their mothers were pregnant with them. A control group consisted of 168 subjects whose fathers had died during the first year of their children's lives **after** birth. Significantly more schizophrenics were found in the index than the control group, a difference that could not be explained by differences in the overall obstetrical complication rates, which were actually higher in the control group. Additional research into the biological and psychological components of prenatal stress and their relationship to schizophrenia seems warranted.

INFECTIOUS PROCESSES

A higher prevalence of schizophrenia in the lower socioeconomic classes has been a consistent finding in studies conducted in England, Europe, and North America, and several hypotheses have been offered to explain this phenomenon, including genetic drift, parental rearing patterns, and psychological stressors which may be associated with lower socioeconomic class. There are certain biological hazards which should also be considered. As Kohn (16) has pointed out, the correlation between prevalence of schizophrenia and lower class status is strongest for cities of large size and not discernible in cities with population below 100,000. It is in large cities that the contrasts in living conditions between social classes are greatest, and, in large cities also, the poor live in slums in which are found extremes of crowding, poor sanitation, suboptimal diet, and inadequate medical care that their counterparts in small cities and in the countryside may not experience. To the extent that birth injury, malnutrition, and infection may play a role in the etiology of schizophrenia, the impact of these factors would be exaggerated in the lower socioeconomic class of large cities.

Several infectious diseases, especially those of viral origin, occur significantly more frequently in lower socioeconomic classes (5). Some of these, like cytomegalovirus, are now known to be congenitally transmitted and to lie latent in the central nervous system, eventually producing deafness or mental retardation at a rate which is considerably higher in populations of low income (7). Torrey has recently observed an elevated titre of cytomegalovirus antibody in the spinal fluid of schizophrenic patients (30). A virus-like cytotoxic agent has been recovered from the spinal fluid of

schizophrenic patients (but also from patients with multiple sclerosis and Huntington's disorder) which is not present in normal spinal fluid (2).

There have been reports describing postinfluenzal psychosis. Menninger (23) was impressed by a large number of such cases admitted to the Boston Psychopathic Hospital during or after the great influenza epidemic of 1918. Sixty-seven of these where influenza was thought to be involved had been diagnosed dementia praecox by the staff, and on followup 20 percent of these had become chronically ill. He described the many features of the mental illness which "were not conspicuously different from the usual type of schizophrenia." It is possible that there are viral strains which show a special affinity for the neural systems involved in schizophrenia and produce a disorder with an acute or chronic course depending on the particular viral-host interactions. Where the response is optimal, the infection and the psychosis would be short-lived; an infection which became latent or which elicited an abnormal immune response could be involved in a recurrent or chronic disorder. The types of interaction that are possible between virus and neuron are manifold, and not all of these would produce pathological changes demonstrable by classical neuropathological techniques (19). Viral infections have been described which affect specific neurotransmitter enzymes in neuroblastoma cells without destroying the cells or producing demonstrable morphological change (25).

The hypothesis that viral infections may play an etiological role in some forms of schizophrenia which was suggested by earlier findings (31) has become more plausible in light of these more recent observations. There is need for further research in this area and for further evaluating the recent findings of virus-like agents and specific antibodies in the spinal fluid of schizophrenic patients.

DIETARY FACTORS

Pauling has proposed an imaginative hypothesis which suggests that an average intake of one or another vitamin may be seriously deficient for individuals with a genetic defect in the absorption or use of the vitamin. This has been found to be the case for several rare neurological disorders of childhood where large doses of the vitamin in question are therapeutic. However, his suggestion that this may be true in schizophrenia has not been supported by evidence of comparable quality. The treatment of schizophrenia with large doses of mixed vitamins, trace metals, and, very often, an antipsychotic drug has not been shown by acceptable evidence to be more beneficial in schizophrenia than treatment without a vitamin or trace metal component.

Dohan has proposed another dietary factor in the etiology of schizophrenia, based upon the considerably higher than expected association between schizophrenia and celiac disease. He has also found that the rate of first admissions for schizophrenia which occurred during World War II in various countries were highly correlated with the rates of wheat and rye consumption. It is also interesting that Ireland, which has a rate for schizophrenia three times that of England and Wales, also has a considerably higher prevalence of celiac disease. Dohan's most recent hypothesis is that some forms of schizophrenia may be the result of a genetically induced intolerance to gluten (4).

OTHER PHYSICAL OR CHEMICAL ENVIRONMENTAL FACTORS

A considerable variety of miscellaneous environmental factors have at one time or another been suggested as etiological factors in schizophrenia. These include food additives, food allergens, and lead or other heavy metal poisonings, although there is insufficient evidence in favor of any of these factors to render them plausible at the present time.

RESEARCH OPPORTUNITIES

A rational program of prevention requires the identification of etiological factors and intervention designed to ameliorate them. In the case of schizophrenia, none of the genetic, biological, or psychosocial factors that may be of etiological importance has been sufficiently identified to serve as the basis of specific preventive intervention. Yet, there is considerable pressure at the present time to propose and pursue specific but premature intervention strategies. Such approaches are costly and require many years before their outcome will become apparent; insofar as they divert attention and funds from research on etiology, they are counterproductive. However, the relief of poverty, the eradication of slums, the reduction of perinatal complications, and the compassionate rearing of children are eminently worthwhile goals, whether or not they will lead to a reduction of schizophrenia. The study of such social advances and their effect on the prevalence of schizophrenia constitutes an important research opportunity and need not compete with other necessary research. Pellagra was clearly associated with poverty, but it is fortunate that Goldberger was interested in understanding its more specific etiology and that the Public Health Service supported him. Poverty is still with us, but, as a result of his efforts, pellagra has practically disappeared.

There is a need to reduce the heterogeneity of the syndrome by more detailed and precise clinical observations in association with laboratory and genetically oriented studies that appear capable of circumscribing more homogeneous subgroups. In addition to twin and adoption studies, study of families with a high density of schizophrenia offers important advantages.

Comparison of the environmental histories of schizophrenic adoptees with greater or lesser evidence of genetic predisposition (15) offers unique advantages in elucidating significant environmental variables. The evaluation of parental personality and rearing practices, if that is to be free of confounding genetic and feedback factors and be based upon other than retrospective accounts, would require the longitudinal study of a group of adoptees at high genetic risk, but, since that would be difficult to achieve, an alternative would be a study of child guidance clinic records on adoptees and their adoptive parents in the strategy which Waring and Ricks (32) have used productively with nonadopted children.

Epidemiological studies and comparisons between populations with high and low prevalence of schizophrenia may throw some light on etiology. An important first question would be the respective weights of genetic and environmental factors in accounting for the difference. Although adoption studies might not be practical because of the difficulty of acquiring a sufficiently large sample, twin and family studies may be useful strategies to apply. In Ireland, as compared with England, for example, the respective concordance rates for schizophrenia in MZ twins, or studies of the frequency of schizophrenia in the pedigrees of schizophrenic patients, could indicate to what extent

the difference in prevalence between the two countries may be accounted for by genetic or environmental variables and make possible the further elucidation of each type of variable. A similar strategy could be applied in attempting to account for the high prevalence of schizophrenia in the lower socioeconomic class of large cities. An elucidation of particular environmental variables might be approached by comparing the environments of probands with high and low prevalence of schizophrenic illness in their families.

A sound national strategy focused on the prevention of schizophrenia and the major psychoses would emphasize research designed to elucidate their causes and bring to clinical trial intervention which will reduce those causes when they have been found. It is also necessary to emphasize, however, the likelihood that some of these crucial etiological factors and their pathognomic characteristics will not become evident without the continued accumulation of our base of fundamental knowledge.

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DISCUSSION

Dr. Gottesman: Dr. Kety speaks of heterogeneity as one of the most important issues we face in schizophrenia research and in some other kinds of research. I think we need to say what degree of heterogeneity we have in mind. Does it mean thousands of different kinds of schizophrenia, or two kinds, to illustrate extreme interpretations? When a nongeneticist sees a nonfamilial form of schizophrenia, he/she may think it is clearly a nongenetic kind of schizophrenia. As a counterexample, children with phenylketonuria, with or without a family history, all have the same kind of gene-based PKU.

Dr. Kety: Well, the kind of heterogeneity I am thinking of is heterogeneity of etiology, a diversity of etiological frameworks with a common morbid process.

I think that, if there is some substance to the syndrome of schizophrenia, some unity, then it is likely that there is a common process in the brain which produces the symptoms of schizophrenia. The cause could be a viral defect, a genetic inadequacy in the production of or effective synaptic action of certain transmitters, or perhaps an impoverished development on the basis of environmental and genetic interactions.

It is certainly true, as I mentioned, that family history does not give one a complete picture of genetic predisposition; but for patients with a strong family history of schizophrenia, especially if they have been reared apart, we may presume a genetic predisposition.

As for those with no family history, if there are forms of schizophrenia in which the genetic factors account for very little of the variance, then we would expect those forms of schizophrenia to be in that group.

Dr. Gruenberg: To follow up on that comment: It is agreed that we want to get away from the simple genetic model; but, beside heterogeneity, there are two other ways. One you did mention very briefly, the spectrum of severity. But how about penetrance? Some environmental forces must interact here.

Dr. Kety: Of course, environmental factors influence penetrance, but these sophisticated analyses take that into consideration. One still finds, however, that the existing pedigrees are compatible with polygenic and monogenic modes and varying degrees of dominance. Certainly, there is a genetic and environmental interaction, but the interaction may be different in different kinds of schizophrenia.

PSYCHOSOCIAL RISK FACTORS FOR DEPRESSION

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INTRODUCTION

Accurate case definition and identification are prerequisites to the determination of precise rates and risk factors for depression, and, until recently, the lack of reliable and valid assessment techniques has hampered research efforts in this area. Newly devised structured interviews which provide operationalized criteria for psychiatric diagnoses are currently in use in epidemiologic investigations (e.g., the SADS and RDC of Spitzer et al. and the PSE of Wing et al.). These instruments furnish an objective means for ascertaining the incidence and prevalence of specific depressive disorders in community populations and correlates of these.

Despite previous difficulties in case definition, a large body of literature exists which examines risk factors for depression. A number of these, primarily of a psychosocial nature, have been identified and include sex, early parental bereavement, poor social supports, recent interpersonal loss, lack of a confidante, and certain personality features.

This paper presents a review of the research on psychosocial risk factors for depression. Risk factors are reported as they relate to depressive symptomatology, nonbipolar depressive disorder, and bipolar depressive disorder. This division is made on the basis of evidence which supports a distinction between symptoms of depression and the syndrome of depression and, with the syndrome, a distinction between at least bipolar and nonbipolar subtypes.

SOCIODEMOGRAPHIC CHARACTERISTICS

Several epidemiological investigations provide evidence that differential rates of depressive symptomatology and the depressive syndrome occur within subgroups of the general population defined by various sociodemographic characteristics.

Sex

An overwhelming number of studies of depression in Western culture report a significantly higher rate of depression in women than in men, with a ratio of two to one typically found in both community survey populations and in diagnosed and treated cases. When cases of depression are broken down by diagnostic category, the female-male ratio is lower in bipolar depressives (1.2 to 1) than in unipolar (2 to 1). Results of community and case register surveys in other Western countries are, by and large, consistent with the U.S. findings, despite distinct differences in definition and measurement of depression (1).

Various hypotheses have been offered to explain these differential rates. Weissman and Klerman (24) reviewed the literature relevant to these hypotheses and came to several conclusions. First, the male-female difference in rates of depression is real and not merely an artifact of corresponding sex differences in rate of help-seeking behavior, since women preponderate not only in studies of treated cases of depression but also in community surveys in which most "cases" have not sought help.

Second, although women do not appear to experience more stressful life events nor consider specific life events as more stressful than men do, at similar levels of stress women report significantly greater intensities of symptoms. One explanation of this finding is that women may be more willing than men to admit to symptoms or, not inconsistently, that men may express their symptoms in different ways—through alcohol abuse or "acting out," for example.

Third, while there is some evidence to suggest that the post-partum period with its associated biological and psychological changes represents a period of increased risk of depression among women, there is little evidence to support the notion that the increased prevalence of clinical depressive states in women is primarily a function of endocrine differences. Furthermore, analyses of incidence figures provide no support for the existence of a separate and distinct "involutional" depressive syndrome in menopausal women.

Finally, personality factors and social role expectations and conflicts appear to be likely candidates for predisposing women to depression. The lesser amount of power enjoyed by women in our society, coupled with higher levels of dependency and passivity, may lead to chronically low levels of self-esteem and decreased ability to cope with stress. These factors, in turn, may increase women's susceptibility to depression.

Age

Recent community surveys are in agreement in reporting higher rates of depressive symptomatology in young adults (aged 18 to 44) relative to older adults. In addition, Weissman and Myers (26) report that peak prevalence of depressive symptomatology in women occurs in those under 35, while peak prevalence in men occurs in the 55 to 70 age range. However, Ilfeld (5), using a different definition and measure of depression, reports that levels of symptomatology are higher in young men age 18 to 24 than in any other subgroup.

Consistent with the findings from community studies, available evidence from clinical studies suggests higher rates of the depressive syndrome in younger age groups than in older. In an ongoing study of a heterogeneous group of depressed and manic patients, the NIMH Collaborative Study group has found that 68 percent of the 325

patients sampled thus far are under the age of 40. Moreover, the peak age of initial episode of the depressive syndrome in these patients is reported to be 22 (NIMH-CRB Collaborative Program on the Psychobiology of Depression, unpublished data).

Age of onset of initial depressive episode differs among various depressive subtypes. Reports from clinical investigations reveal that bipolar depressive illness has an earlier age of onset (late twenties to early thirties) than does unipolar depressive illness (late thirties). Within unipolar disorder, an earlier age of onset has been reported for females than for males. In his study of a clinical population, Perris (18) found 39 to be the average age of first depressive episode for women, whereas 49 was found to be the average for men.

Social Class

Whether defined by occupational, income, or educational level or a combination of these, rates of depressive symptomatology are significantly higher in persons of lower socioeconomic status than in persons of higher social class (25,26). However, Ilfeld (5) found that, while higher in women than in men, overall depression rates were not significantly different in men and women of the lowest socioeconomic classes.

Race

Although a higher prevalence of psychiatric impairment in blacks than in whites has been reported, the impairment has not been limited to depression, nor have the effects of race in these studies been analyzed apart from the confounding influence of social class. Community investigations of the relationship between rates of depression and race have consistently demonstrated that no difference in these rates exists when social class is taken into account (e.g., 5,25,26).

Religion

No differences in rates of depressive symptomatology or in nonbipolar depression have been reported among members of different religious groups; however, bipolar depression has been found to be more prevalent in members of certain religions. Among the Hutterites, a small inbred community of Anabaptists in the northern Midwest, the incidence of bipolar depression is four times that of schizophrenia—a reversal of the findings for the general U.S. population in which schizophrenia is far more prevalent than bipolar depression. In a similar vein, bipolar depression has been reported to be much more common among the Ashkenazi Jews than among Sephardic Jews and other non-Jewish groups (9). In both of these cases, the increased prevalence of the disorder is presumed to reflect the operation of genetic factors.

Marital Status

Differential rates of depressive symptomatology have been reported among various marital categories. Generally, separated and divorced persons show the highest rates of depression, and the never married and presently married show the lowest. Within the latter groups, rates are lower among the married individuals than among singles.

Differing rates of depression for men and women have been reported with regard to marital status (5). Ranked from lowest to highest, depression rates show the following distribution when broken down by sex and marital status: (1) married men; (2) married women; (3) single and widowed women; (4) single, widowed, and separated/divorced men; and, (5) separated and divorced women. Thus, women report higher levels of depressive symptomatology than men in all marital groups, with the exception of single and widowed women whose rates are lower than those of their male counterparts.

Summary

The results of the psychiatric epidemiological and clinical studies of the relationship between sociodemographic characteristics and depression may be summarized as follows: A higher risk of depression exists for females of all ages and all marital statuses (with the exception of singles and widows); there is some evidence to suggest that increasing age and marriage afford some protection to women against depression; for men, however, even greater protection is offered by marriage, whereas age increases their risk; and, finally, the poor of both sexes, all ages, all marital statuses, and black or white are at higher risk for depression than their upper class counterparts.

With regard to the predictive significance of these variables, although the above-described sociodemographic characteristics have been identified as risk factors in depression, these unrefined categories, taken together, account for only 7 to 13 percent of the variance in depression (5,19,23). This demonstrates that no subgroup or combination of subgroups defines those environmental factors which are necessary and/or sufficient to the development of depression.

CURRENT FACTORS

Life Events

Studies of the prevalence of psychiatric symptomatology in community populations support the hypothesis that life events contribute to the development of such disorders. Some epidemiological surveys report a positive relationship between level of psychiatric impairment and number of life events experienced in the months prior to interview (10,12). Moreover, fluctuations in symptom levels and reported number of life events have been shown to correlate positively over time.

The findings reported in clinical studies of the relationship between occurrence of life events and the onset of the depressive syndrome are consistent with those from community surveys reporting an association between life events and psychiatric symptoms. In general, investigators have found that depressed patients experience more life events in the 6 months prior to onset than do subjects from the general population and other psychiatric groups (2,16). Few studies have attempted to differentiate diagnostic subgroups of depressives on the basis of life events. Two groups of researchers examined the relationship between a positive family history of depression and the occurrence of life events (14,22). No significant differences in event rates were found between bipolar and unipolar depressives or between endogenous and reactive depressives in these studies.

Interpretation of the findings in the life events literature is hampered by the recognition that life events may be the consequence of or the cause of a psychological disorder, or confounded with it. To demonstrate a causal effect of life events in depression, they must be shown to: (1) antedate onset; (2) be independent of the disorder, not an indication of insidious onset; and (3) be specific to the depressive disorder rather than arousing generalized stress. The first two of the three requirements of causality are clearly satisfied in studies by Brown et al. (2) and by Myers et al. (12). Brown and his colleagues carefully dated depressive onset and the occurrence of each event in their clinical sample and obtained independent corroboration in each case. Myers and his associates analyzed changes in symptom level in their community sample as a function of independent life events. For each of the events so categorized, recent occurrence was related to higher levels of symptoms.

Epidemiological and clinical investigations have addressed the issue of event-specificity, the third condition required for inference of causality. Nonmutually exclusive event categories have been constructed from the typical listing of life events. When events are broken down into such categories, investigators have shown that the onset of depression is related to distinct types of events. Specifically, it has been shown that depressives experience significantly more "markedly threatening" life events (2), more "exit" events (6), and more "undesirable" events (16) than do normal or schizophrenic controls. Further, Paykel and Tanner (17) demonstrated that the occurrence of "undesirable" life events is associated with the relapse of depressive patients.

The results of these investigations provide evidence of specific types of life events being associated with depressive onset. However, while the weight of the evidence appears to favor a causal role of life events, this support must be viewed in perspective. A problem of interpretation arises when the strength of the relationship between occurrence of events and onset of depression is assessed. Most investigators in the area fail to report correlation coefficients obtained between events and onset of depression. When reported, however, these correlations range from .09 to .30, indicating that such events account for only 1 to 9 percent of the variance in depression. Such figures appear clearly to call into question the predictive significance of specific life events in depression.

Furthermore, the finding revealed in the research to date on life events—that depressives experience more and different types of life events than do control groups—does not provide an accurate estimate of the magnitude of risk associated with these events. All of the clinical research described has been of a case-control nature. That is, the number and nature of life events experienced by a group of depressed patients are compared to those experienced by groups of matched controls. However, to evaluate the efficacy of life events as predictor variables, rates of depression must be analyzed in populations experiencing the life events of interest.

To date, few such cohort studies have been conducted to investigate the role of life events in depression. Clayton, Halikas, and Maurice (3) studied a group of 109 widowed persons and found that 35 percent met their criteria for depression. Paykel (15) has calculated the coefficient of "relative risk" for exit events, which is the product of the ratio-of-illness rates between those exposed to a risk factor (life event) and those not exposed. He estimates that 9 to 10 percent of all exits are followed by depression, which translates into a relative risk of 6.5 for exit events in depression. While such figures are far from impressive, they do suggest a significant role for life events in the development of depression for those exposed.

In passing, it should be noted that an increased risk of depression has been found to be associated with another category of life events: the presence of medical and/or other psychiatric illness, such as drug abuse, alcoholism, Briquet's syndrome, etc. (7).

Personal Resources

From the summary of the life-events literature, it is obvious that life stress is neither a necessary nor a sufficient cause of depression. Since a simple stimulus-response model does not accurately reflect the relationship between life stress and depression, other variables must contribute to depression, possibly by interacting with life stress so as to mediate its effects as well as providing an independent contribution.

One set of variables which are thought to have an effect on the individual's susceptibility to depression is personal resources. Personal resources refer to current interpersonal and extrinsic factors, such as family ties and relationships with significant others, which can serve as support systems in time of crisis. Although intuitively appealing, little work has been done to examine the influence of these variables on the occurrence of depressive symptomatology or clinical depressive disorders.

Myers, Lindenthal, and Pepper (11) explored the relationship between life events and psychiatric symptomatology as a function of sociodemographic and role performance characteristics in a community sample. These investigators found that persons with low events but high symptoms were more isolated, of lower socioeconomic status, unmarried, and dissatisfied with their job or their role as housewife. The authors conclude that these findings support the notion that integration within a social network enables persons to cope better with the impact of life stress.

The finding by Myers et al. (11) that marriage serves a protective role in moderating the influence of life events is supported by results of others who have found that lack of a confiding relationship is a significant mediator of the impact of life events. Women who enjoy a close relationship with a significant other are less likely to report high levels of depressive symptoms in the face of high numbers of life events than are women with high life events without such a relationship.

An independent contribution of personal resources to depressive symptomatology has also been found in community populations. Warheit (23) reports that low socioeconomic status (SES), absence of a spouse, and the absence of friends correlated with high loss scores and high depression scores in his investigation. Furthermore, Warheit found that such personal resources were better predictors of depression than were loss scores.

The lack of personal resources, therefore, appears to increase the likelihood of depressive symptomatology. The actual nature of the contribution made by such factors is unclear, however, for a number of reasons. First, in many of these studies, level of "psychiatric impairment," not depressive symptomatology, was assessed. Personal resources may be interpreted in this context, therefore, as only a nonspecific factor. Second, a conceptual problem arises in the distinction between "personal resources" and "life stress/events," since the difference between the two is often blurred. That is, a lack of personal resources—for example, lack of a close, confiding relationship or low SES—can easily be fitted into a life-stress interpretation (i.e., marital and economic stressors). Thus, the addition of personal resources as a determinant of depression may do nothing to improve predictability. Finally, another problem of interpretation arises

with regard to the issue of cause and effect. Lack of a confiding relationship, the absence of friends, low income level—in short, the lack of personal resources—are just as likely to be the result of the depressive disorders as the cause.

Summary

In light of the interpretive problems which exist in the current factors research, an accurate assessment of their role in the etiology of depression is, at best, difficult. It would appear that life stress, whether defined by the occurrence of discrete events, lack of personal resources, or the operation of ordinary "stressors of living," is greater in depressives than in normal controls. The degree to which this is a cause rather than an effect of the depressive disorder and the degree of specificity and significance of such stressors to depression are issues as yet unresolved. The current status of this literature, however, suggests a relatively minor and nonspecific role of life events and personal resources when assessed independently of other factors.

PERSONALITY CHARACTERISTICS

The importance of personality characteristics in the etiology of depression has been emphasized in various theories of depression, although disagreement exists with regard to terminology and the etiology of the characteristics themselves. In general, these theories postulate the existence of a depressive personality type characterized by low self-esteem, low frustration tolerance, and increased dependency on others for support and approval. These characteristics act to sensitize the individual to situations involving loss of self-esteem—for instance, rejection or loss of a loved one—putting him at higher risk for depression. As such, personality factors are viewed as predisposing factors which render an individual vulnerable to certain stressors.

Despite the considerable theoretical and clinical interest in the role of personality characteristics in depression, relatively few wide-scale, controlled investigations have been conducted in the area. Undoubtedly, the lack of valid and reliable assessment devices and diagnostic criteria has contributed to the lack of research.

Two clinical studies provide details regarding the characteristics descriptive of depressed individuals. Hirschfeld and Klerman (4) compared the scores of 119 depressed patients, on a variety of personality inventories, to the published norms for these scales. Different personality "profiles" emerged for depressed and manic patients. Depressed patients score significantly higher on introversion, neuroticism, and obsessionality. These findings support the notion of abnormal personalities in persons with affective disorders and are consistent with previous research.

Strandman (21) investigated the occurrence of various psychogenic needs, derived from Murray's theory of personality, in a sample of 103 depressed patients. Neurotic and unclassified depressives reported greater need to maintain self-esteem through support and approval from others, greater experience of guilt feelings, and a lesser need to dominate and be aggressive than did bipolar depressives.

Support for the hypothesis that depressives are vulnerable to the impact of certain types of life events (i.e., "loss" or "exit" events which symbolize rejection) due to early childhood experiences is offered in studies of the childhood of depressives and the home

environment of depressed children. In a review of the literature in these areas, Orvaschel, Weissman, and Kidd (13) report that the family home environment of depressed children has been found to be similar to that reported retrospectively by adult depressed patients. These homes are characterized by family discord, parental rejection, and a generally disruptive, negative home environment. An association has also been reported between parental loss in childhood and adult depression. However, the results in this area are inconsistent (8,13), and no definite conclusions can be drawn at this time concerning the etiological significance of early parental loss in depression.

Summary

Taken together, the results of studies of the background characteristics of depressives are consistent with major personality theories of depression. Depression has been found to be an enduring condition in some individuals, persisting despite the lack of identifiable stressful precipitants. The traits which have been found to be associated with depression (i.e., neuroticism, introversion, obsessionality, dependency, and guilt) suggest that depressives are more worrisome, less socially adept, more insecure, more sensitive, and more likely to break down under stress than persons displaying such traits to a lesser degree. Furthermore, the finding that significantly more depressives than normals experience early parental rejection, added to the reports from the life events studies that depressives experience significantly more loss events prior to onset than do normals, fits well with a psychodynamic interpretation of depression.

An association between depression and certain personality characteristics, such as that demonstrated by the above-described research, does not indicate that these characteristics necessarily predispose the individual to depression. Alternate explanations of the relationship may be offered: (1) The depressive disorder and the displayed personality traits may be manifestations of the same underlying genetic or constitutional processes; or (2) the experience of the depression may alter personality characteristics. However, these investigations do suggest a significant contribution of background characteristics to the etiology of depression and indicate that a major improvement in the prediction of depression could result by their inclusion in future research.

CONCLUSIONS

Despite serious methodological problems, psychosocial research findings in affective disorders are remarkably consistent. We can, therefore, draw several conclusions about these risk factors.

First, with respect to sociodemographic characteristics:

1. A greater prevalence of depression is reported in women in both clinical and community research. Within diagnostic subgroups, the male-female discrepancy holds, although the difference largely disappears in bipolars. These appear to be true differences, but the actual causes of the female preponderance in depression are unknown.

2. An inverse relationship between social class and depression rates is consistently reported in clinical and community studies, and no racial

difference in rates is apparent when the social class variable is taken into account.

3. An inverse relationship between age and depression is found in diagnostic groups, with bipolars showing earlier age of onset than unipolars.

4. Married persons are consistently found to have lower rates of depression than nonmarried persons.

In ordering these factors in terms of greatest to least risk presented, sex represents the greatest risk factor, followed by marital status, then social class, and, finally, age. More instructive than the main effects, perhaps, are the interactive effects of sociodemographic variables. The relationship between each of the sociodemographic characteristics and depression described has been reported to vary by sex. Such interactions deserve increased attention in future research.

Second, with regard to life events findings:

1. Within community populations, a positive relationship between number of life events and level of symptomatology obtains. However, the symptomatology investigated in such studies is most often of a general nature and not specific to depression.

2. Within clinical populations, depressives experience a greater number of life events, particularly in the month prior to onset, than do controls, including schizophrenic controls. Differences in life-event rates have not been found for diagnostic subgroups. However, few studies have examined such subgroups.

3. Undesirable events, exit events, and events out of the individual's control are particularly associated with depression.

The actual risk associated with individual events is unknown at present.

Third, personal resources, in the form of a marital or similar relationship, have been shown to serve a protective role in mediating the impact of life events. Because the importance of the contribution of such resources is largely unknown, there is a need to examine them in future research in terms of their role as chronic stressors and social supports.

Finally, personality factors, while occupying a prominent role in theories of depression, have not been included in major research projects. Some characteristics, such as dependency, low self-esteem, etc., have been found to be associated with depression, but little else can be said about these factors at this time.

A basic problem plaguing this area of research has been the reliance on a univariate approach to both predictor and criterion variables. First, depression is all too often treated as a broad, single entity. Most investigators today consider depression to be a heterogeneous group of disorders which differ with regard to onset, symptomatology, and course. It follows that different depressions may have different etiologies. Studies of the effects of psychosocial variables which fail to take into account the multidimensional nature of depression may, therefore, obscure results.

Second, depression in a single individual is the result of a complex interplay of environmental and host factors which include psychosocial, biological, and other domains. Stated simply, depression is a multidetermined disorder. Therefore, anyresearch effort which assesses the predictive significance of some single factor cannot hope to account for any appreciable portion of the variance in depression.

The psychosocial factors discussed in this paper—life events, current social stressors and supports, and personality characteristics—are clearly interactive. Therefore, investigators must approach the study of depression from a multifactorial perspective, both in concept and in research design.

What appears now to be called for in psychosocial research in depression is a series of prospective studies which include a broad coverage of dependent variables and which treat the various depressions as outcome or criterion variables. In conjunction with the application of discriminant function and multiple regression analyses, such designs can best explore the nature of the relationships among psychosocial variables in depression. Alternatively, experimental controls can be incorporated which hold known risk factors, such as sex and biological variables, constant while allowing psychosocial variables to vary, and vice versa. For example, relatives, matched with regard to biological variables but whose psychosocial history and present situation differ, could be compared, as could persons with similar psychosocial histories but very different biological backgrounds. Naturally occurring "experimental" groups could also be studied, such as victims of disasters, persons undergoing rapid life transitions (e.g., adolescents), etc. Such research will permit causal inferences to be made regarding each factor, the assessment of the significance of each of these, and an explication of the process whereby the factors interact.

NOTE

1. The depressive syndrome is defined as a psychiatric disorder in which the major feature of the clinical picture is dysphoric mood or pervasive loss of interest or pleasure accompanied by a number of the following symptoms: sleep and appetite disturbances; loss of energy; psychomotor retardation or agitation; feelings of self-reproach or excessive or inappropriate guilt; reduced ability to concentrate; recurrent thoughts of death or suicide, including suicidal behavior; loss of interest or pleasure in usual activities including social and sexual activities. Bipolar depressive disorder is differentiated from nonbipolar by a history of at least one manic or hypomanic episode (20, pp. 16-17).

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DISCUSSION

Dr. Gershon: We did an epidemiologic study based on a register of all patients admitted to psychiatric hospitals in Jerusalem from 1969 to 1972. In a multiple regression analysis on depression and manic depressive illness, we found the usual correlations. Higher social class, being female, ever married, older, and being an immigrant or disadvantaged ethnic group were associated with affective illness. But, when we did a multivariate analysis we were able essentially to factor out ethnicity, immigration, and socioeconomic status because the populations from which patients were drawn had different age structures. Although the variables were correlated with affective illness, they did not appear to be of fundamental importance. The main predictor of vulnerability seemed to be being female.

Dr. Marks: To what extent have the studies reporting life events separated depressive symptoms from anxiety symptoms? In primary-care studies one commonly gets reports of a general dysphoric anxiety-depression syndrome.

Dr. Hirschfeld: I do not know of any studies of the syndrome designed to look at depression in the absence of anxiety. In the community surveys one could look at the extent to which life events correlate with the anxiety measure as opposed to the depression measure, but I do not recall any discussion of this.

Dr. Klerman: In our study of 220 cases in New Haven (Klerman, Paykel, and Prusoff in Psychopathology and Psychopharmacology, Johns Hopkins Press, 1973, pp. 177-189), I believe that about a third of the cases which we diagnosed as depressed, the clinic had diagnosed as anxiety neurosis. There was an effort in those studies to disentangle anxiety from depressive states, particularly in a paper by Prusoff and myself

(Archives of General Psychiatry, 30:302-309, 1974). It is a good point because there is a correlation of about 0.6 between anxiety scales and depression scales, and you get a compounding of intensity level in profiles.

Dr. Barbara Dohrenwend: We have been finding in our work that you cannot separate anxiety from depression or from a number of other factors that seem to be consistent with Jerome Frank's concept of demoralization. In the community studies, I think we are not really talking about depression in the same sense as in the studies of patients.

I also want to add to your comment that we have estimates of the probability that a depressed person will have life events, but not the other way around. Actually, Gene Paykel attempted to make such an estimate on the basis of some assumptions. The events he called "exits" were strongly associated with depression. Turning it around, he estimated that no more than 10 percent of "exits" would be followed by depression.

SOMATIC FINDINGS IN AFFECTIVE DISORDERS: THEIR STATUS AS RISK FACTORS

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INTRODUCTION

All facets of clinical research in psychiatry contend with the heterogeneity of their common subject matter. Indeed, a central task of research is to account for the variance encountered in psychiatric patients, whatever variables are examined. To reduce the variance in diagnostic categories, a variety of approaches is employed. This includes: nosological studies, pedigree studies, pharmacological response studies, and somatic studies. Somatic studies are addressed to subsystems of the organism. They include studies based in biochemistry, neurophysiology, and neuroendocrinology.

Nosological studies attempt to refine nosology; improved diagnostic categories then serve the traditional medical functions of diagnosis, prediction of treatment responses, and prognostication. Pedigree studies, pharmacological response studies, and somatic studies serve these goals as well. In psychiatry, however, they are traditionally dependent on descriptive diagnosis as a starting point. Thus, the value of an efficient nosology must be apparent. To a large extent, it has been the advent of more or less specific treatments and the elucidation of somatic findings that have stimulated a renaissance in descriptive nosology. Nosology, in turn, has depended on pedigree studies, drug response studies, and somatic studies: It has reached out to them, as it were, to test its validity.

Despite advances in all realms of research pertaining to affective disorders, many problems remain, such as the needs for improved treatment and for prophylaxis of relapse. Solutions probably lie within the realms of pharmacology and possibly neuroendocrinology. Other problems may find resolution from the identification of risk factors. Such needs include early recognition and prevention, differential diagnosis, recognition of masked depression, and identification of affective equivalents (1).

For us, a risk factor is any feature pertaining to an unaffected subject that reliably predicts that he, more than another member of the general population, is likely to become affected. By definition, a risk factor cannot be state dependent. It must be

trait dependent, though, of course, it will persist and accompany the state. Risk factors may be extrinsic to the subject—being in a northern climate in spring or fall is an example (25)—but we are concerned only with risk factors intrinsic to the subject. Risk factors can be historical as in childhood bereavement (31), but we are concerned only with contemporary risk factors. A potent risk factor for affective disorder is membership in an affected family, but this is the purview of pedigree studies, and we are concerned only with drug responses and somatic findings. Risk factors may be evokable or observable in the unperturbed organism, and we are concerned with both. Risk factors may or may not be related to etiology.

A biological finding is a risk factor when it is a trait marker. Psychiatry has a special need for trait markers for, while life events clearly can contribute to the precipitation of illness, lifelong morbidity, probably related to genetic predispositon, is the hallmark of the major disorders.

Both state markers and trait markers can be usefully assessed as to their sensitivity and specificity. High sensitivity exists for a trait marker when a high proportion of the subjects who show it **become** affected, for a state marker when a high proportion **are** affected; high specificity occurs for a trait marker when few subjects who do not show it **become** affected, for a state marker when few subjects who do not show it **are** affected. For both trait and state markers, predictive value will be greatest when sensitivity and specificity are high (2).

A caveat must be entered concerning specificity. Specificity, unlike sensitivity, implies a comparison, and it is important for any variable to know what comparisons have been undertaken. In affective disorder research, comparisons of somatic findings often have been made between unipolar and bipolar patients. When sensitivity has been high in one of these groups but not the other, specificity often has been implied, or the reader at least has been invited to infer it. In fact, in such a case, specificity has been shown only between two groups of depressed patients and not between a group of depressed patients and other mental patients, other sick people, or people generally.

NEUROPHYSIOLOGICAL VARIABLES

There have been many different neurophysiological approaches to patients with major affective disorders. Measurements of the galvanic skin response, eyetracking, continuous performance tasks, and, importantly, average evoked responses have been performed in depressed patients. These data are thoroughly reviewed by Coursey and Buchsbaum elsewhere in this volume. Here we pay attention to variables of disordered sleep.

Hartmann (20) and Kupfer (26) recently reviewed in detail sleep data in affective disorders. In short, sleep-pattern disturbances can be sorted out into difficulties in falling or staying asleep; changes in total sleep or total sleep requirement; and changes in specific sleep stages, namely slow-wave sleep and D-sleep (desynchronized sleep or REM sleep). Poor sleep can accompany many psychiatric and medical diagnoses, and a "sleep marker" with both high specificity and sensitivity for major affective disorder still awaits description.

Late insomnia (early waking) is a characteristic finding in many, though not all, depressives. However, as pointed out by Hartmann (20), one needs to keep in mind that

late insomnia can be observed in a variety of conditions such as "sleep apnea, nocturnal myoclonus, schedule disturbances, certain drug dependencies and in (several) medical conditions. . . ."

Evidence from several centers (20,21,26) shows that severely depressed patients experience a reduced amount of slow-wave sleep. Some studies indicate that it may remain reduced for several months. However, specificity of this finding for depression is rather low. It can also be found in acute stress and anxiety as well as in chronic schizophrenia (20). One theory holds that reduced slow-wave sleep is a nonspecific indication of generalized central hyperarousal, as may occur in severe depression, anxiety, and schizophrenia (5).

D-latency is defined as the amount of EEG-synchronized sleep preceding the first desynchronized period. D-latency has been reported to be shortened in depressed patients (20,26). Kupfer (26) reported a significant negative correlation between D-latency and severity of depression. Reports from the same laboratory indicate that shortened D-latency may be useful as a marker for primary depression. As compared to patients with secondary depression, patients with primary depression showed significantly shorter D-latencies. The finding held in inpatients and outpatients and was not a function of age (26). It is important to note that the specificity of this finding for primary depression has not yet been established. For example, increased stress is also associated with decreased D-latency. Hartmann (20) thinks that D-latency is negatively related to psychic pain and stress rather than to depression per se.

Taken together, the data indicate that there is no sleep variable whose specificity and sensitivity are such as to render it an efficient state marker, let alone a trait marker, for depression.

PHARMACOLOGICAL VARIABLES

Drug responses distinguish crudely at least, depressed patients from normals. Tricyclic drugs produce favorable changes in the former but have little effect in the latter (24). Conversely, amphetamine may be a more reliable euphoriant in normals than in depressives, though this distinction is not as clear, since a euphoric response to amphetamine has been used to distinguish among depressives (16). Differences in drug responses between normals and depressed patients are often taken as evidence that depression does, in fact, have a somatic substrate.

Drug-response differences clearly exist between categories of depressed patients. Resolution of types based on drug response differences tallies quite well with resolution based on the unipolar (UP)-bipolar (BP) dichotomy proposed by Leonhard (30). Although lithium carbonate is a potent prophylactic agent in both UP and BP patients, most studies, though not all, indicate that lithium carbonate is more often an effective antidepressant in BP than in UP patients (see 1 and 12 for a review).

The induction of a hypomanic or manic state during antidepressant treatment is found consistently more often in BP than in UP patients (12,17). Akiskal et al. (2) found pharmacologically induced hypomania in 10 out of 40 primary depressives (low sensitivity) and 0 out of 60 patients with nonprimary affective disorder (high specificity). When the primary depressives were further separated, 9 out of 18 BP and 1 out of 22 UP patients developed hypomania.

Differences in pharmacological responses have been used not only to test the validity of the UP-BP dichotomy but also to prognosticate regarding the effect of one or another treatment. Thus, for example, Fawcett et al. (16) have shown that a prompt euphoric response to a test dose of amphetamine augurs well for a satisfactory definitive response to imipramine.

BIOCHEMICAL VARIABLES

Metabolism of central monoamines appears to be intimately involved in the process of affective disorders. Various theories attribute importance to changes in catecholamines (39) or indoleamines (11), or to some combination of the two (37). In this review we focus on data relevant to monoamines that may be of some predictive or diagnostic value (18).

Three studies have addressed urinary 3-methoxy-4-hydroxyphenylglycol (MHPG) in depressed patients. Goodwin and Beckmann found MHPG to be significantly lower than normal in BP patients. UP patients showed higher values than normals, but not significantly so. Maas et al. found urinary MHPG to be equally lower than normal in both UP and BP patients. Schildkraut reported lower MHPG values in BP, as compared to UP patients (see 18 for a review).

In cerebrospinal fluid (CSF), several authors measured 5-hydroxy-indoleacetic (5-HIAA) and homovanillic acid (HVA), end products of serotonin and dopamine metabolism respectively, before and after probenecid administration. Probenecid inhibits the transport of these metabolites out of CSF; therefore, their measurement before and after the drug is thought to provide an index of their rates of synthesis.

No finding pertaining to monoamine metabolites in CSF has been so clearly established as to allow the differentiation of UP and BP patients. Nor, on these parameters, are the two forms of primary depression clearly distinguished from controls (18).

NEUROENDOCRINE VARIABLES

Recent major advances in neuroendocrinology have greatly enhanced our understanding of the intimate relationships between the nervous system and the endocrine system. Thus, for example, it is now generally accepted that the brain influences anterior pituitary function through the release of so-called hypothalamic hypophysiotropic hormones (HHH).

Growth Hormone (GH)

In contrast to other pituitary hormones like thyroid stimulating hormone (TSH) or luteinizing hormone (LH), GH lacks a specific end organ. GH secretion is regulated by a complex interaction of stimulating (GH-releasing hormone) and inhibiting (GH-inhibiting hormone, somatostatin) influences. Factors such as stress, exercise, sleep, and hypoglycemia, among others, are thought to play a modulating role (7,14).

GH secretion in depressed patients has been studied after administration of L-Dopa, TRH, or d-amphetamine, and after insulin-induced hypoglycemia (see 7 and 14 for a review). GH secretion after L-Dopa in depressed patients was found to be impaired in one study, increased in one other, and not different from controls in two others. Equally diverse are the data comparing UP and BP patients.

After insulin-induced hypoglycemia, GH secretion seems to be impaired in patients with primary depression, UP patients, and depressed postmenopausal women, as compared to controls.

TRH does not, under physiological conditions, stimulate GH secretion. There are, however, several pathological conditions in which a GH response after TRH has been observed, viz. acromegaly, chronic renal failure, and anorexia nervosa. Some authors (3,35), but not all (32), have found a certain frequency of GH response to TRH in patients with primary depression.

Langer and his co-workers found the GH response to amphetamine impaired in patients with primary depression and increased in secondary depression (28).

GH secretory abnormalities in depressed patients that can be accepted confidently are limited to those induced by insulin hypoglycemia and TRH. After the former, depressed patients secrete less GH than normal subjects; after the latter, a pathological GH response is seen in some patients.

Prolactin (PRL)

After L-Dopa, PRL secretion was found to be impaired in BP patients, as compared to UP patients in one study but not in another. Insulin-induced PRL secretion in UP and BP patients was not found to be different from controls (see 7 and 14 for a review). After TRH, PRL response in patients with primary depression was found to be diminished in two studies (3,13) and increased in one (35), as compared to normal subjects.

Luteinizing Hormone (LH) and Follicle Stimulating Hormone (FSH)

Two groups have measured the LH/FSH responses in depressed patients. Ettigi et al. (15), using a combined TRH/LHRH injection, found the LH response significantly increased in secondary depression. In contrast, primary depressives did not differ from normal subjects. Amsterdam et al. (3) found LH and FSH responses after TRH injection in a significant number of depressed patients. The latter finding is of special interest since, under normal conditions, TRH does not exert stimulatory effects on LH or FSH.

Thyroid Stimulating Hormone (TSH)

In normal subjects, the TSH response to TRH seems to decrease somewhat with increasing age; women, probably through higher estrogen levels, seem to have a somewhat greater TSH response, as compared to men (see 38 for a review). A blunted TSH response to TRH is generally supposed not to occur in normal subjects, though Anderson et al. (4) reported a low prevalence (4/79) in an early study of young men. In our laboratory we have studied more than 80 normal subjects of both sexes. The lowest

ΔTSH (maximum rise over baseline) found was 5.8 μU/ml. Based on this finding, we defined a blunted TSH response as ΔTSH < 5 μU/ml.

Prange et al. (36) first reported that a fraction of patients with primary depression show a blunted TSH response after TRH challenge. To date, this finding has been replicated in more than 30 studies involving over 500 patients. We have recently reviewed this mass of data (33), and no clear relationship between a blunted TSH response and other clinical features has emerged. The deficient response does not seem to be related to severity of depression or age. Some authors found the mean TSH response to be significantly lower in UP as compared to BP patients, while others did not find such a difference. Prolongation of the depression process may increase the frequency of blunting, but this had not been confirmed.

It is important to note that a blunted TSH response is not specific for mental depression. The fault is a diagnostic feature of hyperthyroidism. It has been observed in Klinefelter's syndrome, 36-hour starvation, excess somatostatin activity, chronic renal failure, Cushing's disease, heroin addiction, and after glucocorticoid or L-Dopa administration (see 33 for a review). These factors have been excluded in depressed patients, with one exception. We have recently reported that in some depressed patients TSH blunting is adequately accounted for by serum cortisol elevation (34). Disturbances in cortisol secretion have been widely described in depressed patients (10); these disturbances, however, are usually related to the state of depression and tend to normalize when clinical recovery occurs. TSH blunting, in contrast, occurs in some patients in remission.

Is TSH blunting related to the state of depression, or is it a trait marker? As stated above, several authors have found the fault in depressed patients in remission. Kirkegaard et al. (23) and Gregoire et al. (19) did find, however, that the event often normalizes with remission. More study is needed to elucidate this question. A recent report by Asnis et al. (5) demonstrated a significantly lower mean TSH response in UP patients, as compared to patients with secondary depression both during depression and after recovery.

Within a psychiatric population, how specific is the TSH response to depression? Our group has recently studied 17 schizophrenic, 12 depressed, and 39 alcoholic patients. Alcoholics were studied in acute withdrawal, in a state of postwithdrawal when all symptoms of acute withdrawal had shown complete remission, and during Alcoholics Anonymous membership with a proven record of abstinence for more than 2 years. A blunted TSH response was found in 6 out of 12 men in acute withdrawal, 5 out of 14 men in postwithdrawal, and 3 out of 13 Alcoholics Anonymous members. In contrast, schizophrenic patients did not show the fault. Taken together, these findings indicate that a blunted TSH response is not merely a nonspecific correlate of mental stress. It also, however, is not specific to depression—some alcoholic patients show the fault whatever their recent drinking behavior. Whether TSH blunting is a somatic correlate of the genetic relationship between alcoholism and depression postulated by Winokur (42) is at present speculative but appears worthy of investigation.

Impaired Cortisol Suppression After Dexamethasone Administration

The functional activity of the hypothalamic-pituitary-adrenocortical (HPA) axis has been studied widely in depressed patients (8,10). Of special interest in the present

context are studies in which the suppressibility of plasma cortisol by oral doses of dexamethasone was examined.

In normal subjects, dexamethasone given as a single dose at midnight suppresses plasma cortisol for at least 24 hours. In earlier studies in depression, some patients were found to have inadequate suppression, though not all investigators agreed (see 8 for a review). As pointed out by Carroll (8), however, these studies used only the 8 a.m. postdexamethasone blood levels. What seems abnormal in depressed patients is an early cortisol escape from suppression rather than an absolute resistance to suppression. To identify "early escape," it is necessary to study the 8 a.m., 4 p.m., and 12 p.m. postdexamethasone plasma levels of cortisol. Using this design, Carroll and his colleagues (8) demonstrated that "with increasing severity of depression, this escape occurs more early on the day after administration of dexamethasone." According to these authors "about half" of the patients with primary depression showed abnormal responses. This has been confirmed in recent studies by Brown et al. (6) and Stokes et al. (41). Langer et al. (29), however, did not find abnormal responses in 10 UP patients, but these patients were treated with diazepam, and the possibility that this has confounded results cannot presently be excluded.

Schlesser has recently reported results of the dexamethasone suppression test (DST) in depressed patients in which the diagnostic classification system suggested by the Iowa group was used (40). In this intriguing study, 23 out of 28 patients with familial pure depressive disease, 13 out of 35 with sporadic depressive disease, and 1 out of 23 patients with depression spectrum disease showed early escape. These data, however, need to be interpreted with caution, since Carroll and his colleagues (9) found that 5 out of 6 of patients with depression spectrum disease showed abnormal responses. Early escape by depressed patients in the DST, whatever its frequency in various subtypes, clearly normalized with remission (8), just as other HPA axis faults tend to normalize. Thus, the event is a state marker rather than a trait marker.

In a psychiatric population, how specific to depression is early escape in the DST? Stokes et al. (41) studied secondary depressives, schizophrenics, and schizoaffective patients. Early escape was shown in 17 out of 36 secondary depressives, 5 out of 29 schizophrenics, and 3 out of 9 schizoaffectives. Carroll et al. (8) studied a psychiatric control group that consisted of patients with such various diagnoses as secondary depression, organic brain syndrome, anxiety neurosis, personality disorder, and facial dyskinesia. The authors concluded that "all patients with depressive neurosis and most patients with other nondepressive disorders had completely normal response to dexamethasone." Brown et al. (6) did not find abnormal responses in patients with schizophrenia (n=8), neuroses (n=9), alcoholism (n=10), or drug abuse (n=2). Lamberts et al. (27), however, described two alcoholic patients and cited nine other alcoholic patients who showed abnormal responses.

SUMMARY

There appear to be a number of risk factors for primary affective disorder with utilitarian value—childhood bereavement and membership in an affected pedigree are examples. However, the somatic findings that we have discussed are not among them. They may, of course, be useful in other ways. Early escape of cortisol from dexamethasone suppression may, for example, distinguish primary depression from schizoaffective disorder. A persistently blunted TSH response to TRH may, for example,

predict early depressive relapse. Moreover, it can readily be imagined how extensions of present work could produce useful risk factors.

Among the somatic findings we have reviewed, there appear to be no findings that presently lend themselves usefully to risk assessment for affective disorder. Yet, with the above consideration in mind, we are astonished by how little has been done with differential responses to common agents. For example, one might consider giving to all members of an affected pedigree one or more of the following substances: L-Dopa, L-tryptophan, imipramine, and d-amphetamine. People do respond differently to these agents, and these differences may well reflect differences between nervous systems, even when disease is not manifest. Dependent variables should include not only global psychological responses but also such changes as those induced in EEG, for example. Here, we recall the work of Itil (22) in describing the EEG changes in normals produced by single doses of common psychoactive drugs.

We may wonder if any single somatic finding, especially if related to cause, can possibly show high sensitivity in a disorder that is probably a syndrome with multiple causes. The other side of this problem is the prevalence of the finding in "normal" populations. Unless a control population is selected to be utterly without risk for affective disorders (negative family history, no childhood bereavement, etc.), a risk factor should occur in "normals" with a certain low frequency, given the prevalence of people who are, in fact, at risk.

Researchers who concern themselves with somatic findings usually have etiology in mind, but their findings can nevertheless be usefully evaluated as risk factors. The other way around, the search for risk factors has identified individuals, viz members of affected pedigrees, in whom the search for etiology can profitably be focused.

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DISCUSSION

Dr. Gottesman: One of the points you made is very important to us who are working on the genetic aspect of these things. If you could find something that was useful for predicting risk **within** a schizophrenic's family, that would be very important. It does not necessarily have to be a valid predictor in the general population to be useful, although it would be better if it did both.

Dr. Regier: I think your focus on specificity and sensitivity of the marker is extremely important. For a general population study, we want to know something about the relative risks. A factor with a risk ratio of 10 is very efficient, and at this level, something like expressed emotionality would be worthwhile to pursue, even though it may take a long time to get the information. This would be very useful for prospective studies. If the difference on a certain variable between patients with a given mental disorder and those without it is minimal in cross-sectional studies, there is much less value in doing longitudinal studies to confirm it. So you have helped to focus our discussion.

RISK FACTORS IN ANXIETY DISORDERS

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In DSM-II, "anxiety disorders" are defined as those in which anxiety is experienced directly. These are a fragment of the earlier DSM-II category of "neuroses," which was renamed and dispersed among several categories in the DSM-III, as shown in table 1. The neuroses were defined as conditions in which the chief characteristics were anxiety either (1) felt or expressed directly or (2) controlled unconsciously or automatically by conversion, displacement, and various psychological mechanisms. The DSM-III category of anxiety disorders is thus smaller than the DSM-II category of neurosis, corresponding only to the first of the two DSM-II definitions. Four of the DSM-II sections of neurosis were subdivided into 11 DSM-III sections of anxiety disorders. Some might feel that certain of the DSM-III subdivisions are too elaborate, e.g., the use of panic attacks to define separate sections and the separation of atypical from generalized anxiety disorder. Hard research is needed to indicate whether such subdivisions have etiological or therapeutic import.

The DSM-II neuroses which are not included in the DSM-III category of anxiety disorders are also seen in table 1. One problem with the classification immediately becomes apparent. The disorders of depression, depersonalisation, hypochondriasis, and even conversion hysteria, despite the traditional view about belle indifference, are commonly associated with much directly experienced anxiety and, to that extent, overlap with the anxiety disorders. Conversely, many obsessive-compulsive and phobia-like conditions are not associated with anxiety but are so classified in DSM-III. Of course, any classification is bound to have blurred edges, and this might be the best classification that we can agree on at the moment, but it is useful to identify where the edges are blurred as this tells us where further research might refine our concepts.

We turn now to issues of potential risk factors for particular forms of anxiety disorders and population subgroups at risk, and to consideration of interventions which might modify some of the risk factors which can be identified. Few prescriptive suggestions can be made at this stage of knowledge, but we can see what ideas emerge from an overall examination of the field.

Table 1. DSM-II neuroses and DSM-III anxiety disorders.

DSM-II NEUROSES		DSM-III EQUIVALENT	
			ANXIETY DISORDERS
300.00	Anxiety Neurosis	300.00	Atypical anxiety disorder
		300.01	Panic disorder
		300.02	Generalized anxiety disorder
300.2	Phobic Neurosis	300.21	Agoraphobia with panic attacks
		300.22	Agoraphobia without panic attacks
		300.23	Social phobia
		300.29	Simple phobia
		309.21	Separation anxiety disorder (in childhood section)
300.3	Obsessive-Compulsive Neurosis	300.30	Obsessive-compulsive disorder
	Not Represented	308.30	Post-traumatic stress disorder, acute
	Not Represented	309.81	Post-traumatic stress disorder, chronic
			OTHER CATEGORIES
300.5	Neurasthenic Neurosis	300.12	Chronic depressive disorder
300.6	Depersonalization Neurosis	300.60	Depersonalization disorder (Dissociative disorder)
300.7	Hypochondriacal Neurosis	300.70	Hypochondriasis
	Not Represented	300.81	Somatization disorder (Hysteria, Briquet's disorder)
300.4	Depressive Neurosis	296.21 or 31	Major depressive disorder, single episode or recurrent, without melancholia
		301.12	Chronic depressive disorder
		309.00	Adjustment disorder with depressed mood
300.13	Hysterical Neurosis		(Concept "hysteria" avoided)
300.1	Hysterical Neurosis, Conversion Type	307.80	Psychogenic pain disorder (Somatoform disorder)
		300.11	Conversion pain disorder (Dissociative disorder)
300.14	Hysterical Neurosis, Dissociative Type	300.12	Conversion amnesia disorder
		300.13	Conversion fugue disorder
		300.14	Multiple personality (in childhood section)
		307.46	Somnambulism (in childhood section)
300.8	Other Neurosis		
300.9	Unspecified Neurosis		

PHYLETIC ASPECTS (SPECIES GENETICS)

Of the biological factors, we will first look at phyletic considerations. Increasing attention has recently been paid to the phylogenetic heritage out of which human behavior evolved. The species has a proclivity to develop fear easily to situations of special evolutionary dangers. Given our daily exposure to an enormous range of stimuli, it is remarkable how narrow a range of these stimuli become the triggers for phobias and fetishes.

The limited and stereotyped range of phobias (and fetishes) which are common in man may be explained by the concepts of "prepotency" and of "preparedness." Prepotency implies that certain stimuli have special salience for the species, while preparedness implies selectivity of response to such stimuli. Prepotency and preparedness are embodied in the phrase "doing what comes naturally." As a result of natural selection, not all classes of events are equally associable either naturally or in the laboratory. In the visual modality, among the central features which elicit fear or withdrawal in vertebrates are stimuli which are abrupt, of high magnitude, and irregular in timing (15).

Phyletic issues not only influence **what** comes to be feared but also **when** this fear will manifest itself. There is abundant evidence that in animals and in man certain types of fears appear especially at certain ages rather than at others, irrespective of the amount of contact with the relevant stimuli. It is well documented, for example, that human offspring avoid perceived heights as soon as they can crawl, show fear of strangers from 6-8 months onward, fear animals maximally between ages 1 to 6, and usually show taste aversion between age 6 to 13 years (16). Such age-linked acquisition independent of obvious environmental factors spotlights the role of maturational influences on acquisition of phobias.

A maturational phase also seems to be present for normal rituals, though its existence remains to be confirmed by systematic research. Anecdotally, normal children between ages 6 and 10 play repetitive games, often tap alternate pickets when walking alongside a fence, avoid cracks in the sidewalk lest harm befall them, and feel compelled to do things in set fashion. These compulsions usually disappear as quietly as they arise, their volatility being similar to that of normal fears in childhood. It is hard to think of any evolutionary reason for such a phase of rituals, and whether it affects the later development of adult compulsions remains speculative.

The clearest experimental demonstration of age-related fear comes from Sackett (23) in rhesus monkeys. These were reared in isolation and shown slides projected onto a screen on one side of the cage in a daily session. The slides showed monkeys in poses including threat, play, fear, withdrawal, exploration, sex, and inactivity. Little disturbance occurred throughout the first months of testing with any pictures except those of threat. Before the age of 2 months, threat pictures did not evoke disturbance (figure 1). However, between 2-4 months of age, markedly disturbed behavior occurred whenever pictures of threatening monkeys appeared on the screen, and this behavior consisted of fear, withdrawal, rocking, and huddling, and each of the different animals behaved similarly to all threat pictures and reduced working a lever to view such pictures (figure 2). Fear responses to threat waned after about 110 days after birth. In rhesus monkeys, general avoidance behavior appears after a period of approach behavior (12), and homologous periods appear to occur in human infants who progress first through a stage of smiling to that of a fear of strangers.

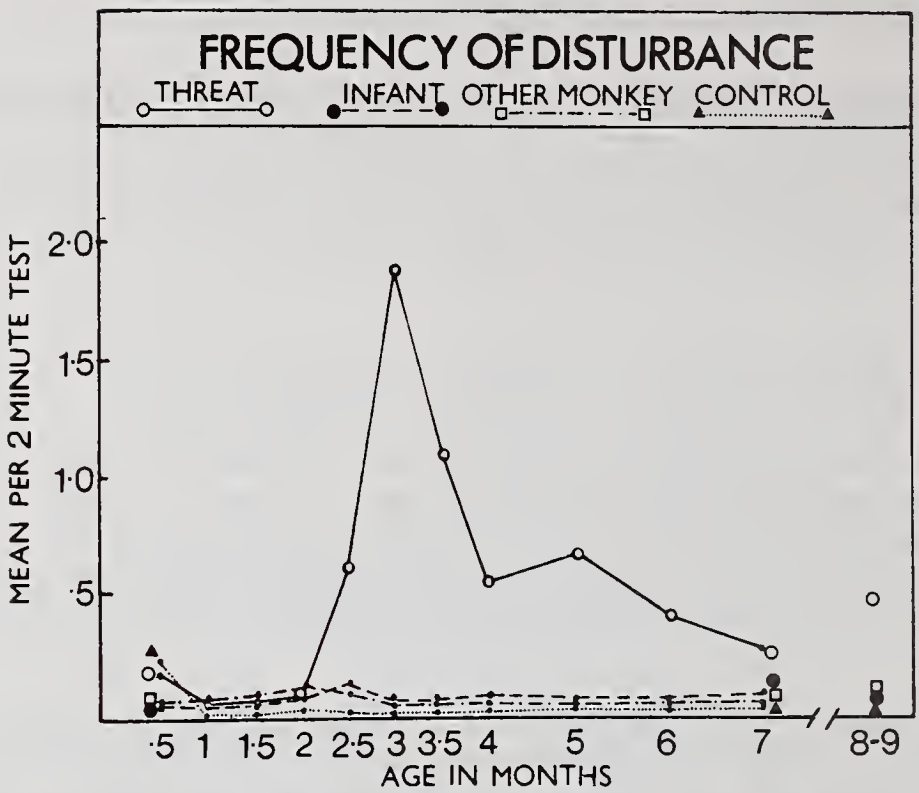

Figure 1. Reactions to experimenter-controlled slides. Fear is evoked only at age 2-4 months and only by threat pictures. Sackett (23). (Copyright 1966 by the American Association for the Advancement of Science.)

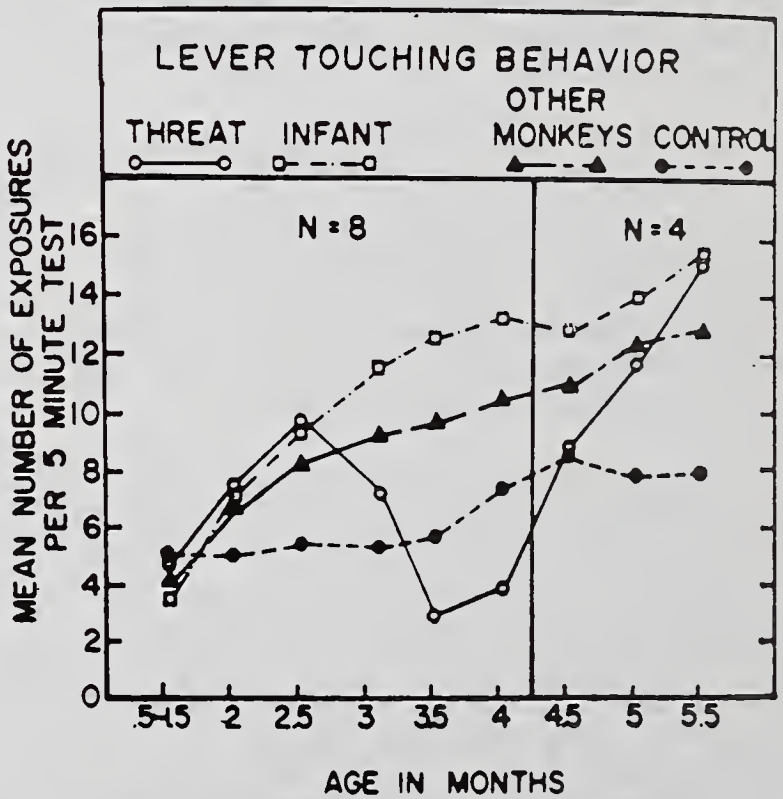

Figure 2. Frequency of self-exposure to slides. Fear is evoked only at age 2-4 months and only by threat pictures. Sackett (23). (Copyright 1966 by the American Association for the Advancement of Science.)

Our understanding of anxiety disorders would be enriched by experiments to determine how approach and withdrawal of various kinds develop for different classes of stimuli. We could slowly build up maps of stimulus-response (S-R) valencies which would indicate areas of human prepotency or preparedness to approach and withdraw from various classes of stimuli. Eventually such maps of natural classes of connected events might yield clues not only to the origins of anxiety disorders but also to better ways of treating them.

A biological contribution to etiology need not necessarily alter the clinician's treatment strategy in this area. Etiology and treatment do not always go hand in hand, and prepared phobias improve at least as readily with exposure treatment as do unprepared phobias (5). Nevertheless, knowledge of the design features of an organism could influence our therapeutic and preventive strategies, as it is easier to work with nature than against her. The notions of prepotency and preparedness are related to the concept of generative grammar which has enriched our understanding of language development and to the notion of a social grammar of interaction which might help us ultimately identify how and when to intervene to prevent or modify problems of social interaction.

A special instance of physiological phylogeny is vasovagal fainting in blood/injury phobias. Usually our hearts beat faster when we are afraid (19), but one phobic situation--blood/injury--seems different from all others examined so far in the readiness with which, despite occasional initial tachycardia, continued contact with the phobic stimulus produces instead bradycardia and fainting suggestive of vasovagal stimulation. The association of bradycardia with blood injury stimuli may be part of a species pattern of autonomic responding which has evolutionary significance. It is interesting that the tonic immobility reaction in chickens, rabbits, and other species is associated with bradycardia (20), but the heart rate during the possibly similar phenomenon of death feigning in possums and other species is not yet clear.

Vasovagal fainting to blood/injury stimuli might reflect not only phylogenetic sensitivity of the species but also genetic susceptibility of certain individuals. An untested impression is that blood/injury phobics have unusually many family members with similar problems. Perhaps these are individuals at the extreme end of a normal continuum of cardiovascular responsivity to tissue damage stimuli, and perhaps this sensitivity may be genetically influenced and predispose individuals to develop blood/injury phobia.

Among blood/injury "phobics," **fear** of blood is often not present, merely nausea, fainting, and habitual avoiding of relevant situations. This points to another area for research into the wiring diagram of the species. Avoidance of different types of situations seems to be associated with different subjective states. Certain patients report that the nausea which is triggered by blood/injury stimuli feels distinctly different from the nausea triggered by taste aversion. This, in turn, is different from the anxiety experienced with most other phobic stimuli and from the disgust or discomfort (rather than anxiety) which is reported by many obsessive-compulsives when in contact with "dirt"; yet other subjective sensations are noted with touch aversions (17). Different classes of avoided situations thus seem to associate with different subjective states. Perhaps this issue is related to the possibility alluded to earlier of building up maps of S-R valencies of human prepotency.

INDIVIDUAL GENETIC INFLUENCES

Individual genetic influences on anxiety disorders are reviewed elsewhere in this volume and will be discussed only briefly here. In animals, selective breeding experiments have demonstrated that emotional behavior, such as aggression and fearfulness, is strongly influenced by multiple genetic factors and is associated with selective biochemical changes. Anxiety-related features which have been selectively bred in animals include, in rats, general level of fearfulness, escape avoidance, and tonic immobility, and in dogs, passive defensive behavior and general fearfulness. Tonic immobility, which can be regarded as an analog of freezing during fear, was increased four times in duration by selective breeding over merely one generation of chickens (8). Similarly, stress-induced fatal hypertension has been selectively bred in rats.

There is a high incidence of anxiety states in families of patients with anxiety disorder, but none of the studies has excluded the effect of familial environment (reviewed by 14, 24). Genetic influences might act by predisposing individuals to have timid or other temperaments leading to later anxiety disorders, a theme to which we will return.

Twin research in the area is suggestive both for personality and for illness. Fear of strangers in twins during the first year of life is more concordant among monozygotic (MZ) twins than dizygotic (DZ) twins, and adult twins show more concordance for "neuroticism" among MZ than DZ even when the MZ pairs have been reared apart. Similarly, physiological responses such as skin conductance, EEG, pulse, and respiration rate are more alike among MZ than DZ twins (13).

For phobic and obsessive-compulsive illness, 43 Maudsley twin pairs were studied where one or both had the diagnosis (1). Carey found a higher concordance among MZ than DZ twins for phobic and obsessive-compulsive **symptoms**, more than for diagnosis of these two disorders. All the concordant phobics were polyphobic (including agoraphobia), not monophobic, and the concordance was for presence of phobic symptoms rather than for the detailed nature of the phobic situation. Another twin study, of 99 same-sex twin pairs (25), also found that MZ twins were more similar than were DZ twins for strength of phobia and for the type of situation which was feared, but this time the effect was restricted to the nonagoraphobic fears.

Studies of genetic risk factors concerning anxiety disorder in man can only yield definitive evidence if undertaken in MZ twins reared apart compared to those reared together so that the environmental contribution can be teased out. Because such tiny numbers are available, such research is only viable if it is undertaken across several centers. Carey's 43 twin pairs constituted the entire relevant Maudsley sample over many decades.

BIOCHEMICAL FACTORS

So far no reliable biochemical correlates of anxiety have been found in man, but there is increasing evidence that peptides affect avoidance responses in mammals (9,21), different peptides overlapping in their behavioral profiles, yet retaining areas of specificity. The time courses of behavioral actions of peptides are intermediate between those of very rapidly acting neurotransmitters and those of slowly acting hormones.

This time course of events is potentially important and has largely been ignored in the behavioral literature, which tends to report brief experimental paradigms over merely hours or days. In contrast, most anxiety disorders tend to come on over weeks, months, or years. A more appropriate time scale is to be found with the neurophysiological phenomenon of "kindling" in rats, cats, and monkeys which might just conceivably be relevant to anxiety disorders. Here, periodic stimulation of sites in the limbic system at intensities initially too low to produce any behavioral or EEG effects eventually produces behavioral convulsions (10). With repeated stimulation, the after-discharge threshold is decreased to the point where subsequent stimulation at previously subthreshold levels now reliably elicits an after-discharge. With continued stimulation, mild motor automatisms appear which gradually increase in severity with each successive stimulation, until motor seizures are elicited. The evidence suggested that some process continued in the brain for more than 12 hours after each 60 seconds of stimulation. The optimal stimulation interval is about 24 hours, and massed stimulation may retard kindling. This stepwise increase over days and weeks is reminiscent of the onset of phobias, obsessions, and anxiety states, and one wonders whether it is worth searching for sensory equivalents to these motor phenomena which might account for the panics seen in certain anxiety disorders.

An intriguing preliminary finding by Curtis et al. (4) well deserves attempts at replication. They found that treatment of phobics by exposure in vivo took double the time to reach criterion of improvement in the morning, when cortisol secretion was maximum than in the late afternoon when cortisol secretion was minimum. If this finding is replicated, the question arises whether this has to do with the biological clocks of the subjects or of the therapist. Such findings could not only influence clinical practice but also raise questions about the differential sensitivities of individuals to stressful stimuli according to the phases of their biological clocks at the time of the stressful experience.

PREMORBID PERSONALITY AND LATER SYNDROMES

Granted that temperament and personality have both genetic and environmental components, some temperaments may facilitate the development of certain anxiety disorders. The cliche that timidity is the soil out of which phobias necessarily grow is often disproved by clinical experience that phobias can develop in the most courageous of people, but nevertheless timidity and perhaps overprotection in childhood might sensitize individuals to develop later phobias. Agoraphobics with a history of school phobia developed their agoraphobia significantly earlier than agoraphobics without such a history, though this could be because the two clinical states are two sides of the same syndrome at different ages, or the one state might predispose to the other, or both might reflect a common third problem (15). Another type of personality—meticulous personality—is often said to be associated with the development of subsequent obsessive-compulsive disorders, even though compulsive rituals can develop in the most slipshod and untidy of individuals. Associations have been found between the presence of hardworking, time-conscious personalities and coronary heart disease, and by that token most of us here today are at risk. Whether this is relevant to anxiety disorders is problematic.

Prospective longitudinal studies can throw light on these questions and would be less expensive if appropriate data were collected as part of a longitudinal study of wider

issues. This area is important to explore with a view to identifying high risk populations for future preventive programs.

PSYCHOLOGICAL AND SOCIOENVIRONMENTAL INFLUENCES

It is not clear which, if any, environmental events trigger anxiety disorders and how far they are necessary conditions for their onset. While certain life events seem to precipitate anxiety disorders, this is also true of many other disorders, e.g., neuropsychiatric admissions of soldiers, neurosis in general practice, and depression (6).

Childhood events are associated with subsequent development of some emotional disorders. Loss of a mother before age 11 predisposes women 20 years later to develop depression. The relationship of emotional disorders in childhood to later anxiety disorders in adult life was reviewed by Cox (3). He concluded that most children with emotional disorders do not become neurotic adults, and most neurotic adults were not neurotic as children, but there is some evidence of continuity.

The association of social dysfunction with the persistence of anxiety and depression was observed by Goldberg and Blackwell (11). Those primary care patients with depression who were still ill at 6 months followup tended to have insoluble life problems, e.g., sick relatives or long-standing personality disorder. Similarly, in the primary care sample of Cooper (2) there was a marked excess of social difficulties among chronic neurotics compared with controls, and the clinical severity of their neurosis was related to their degree of social dysfunction.

The potential importance of social bonds for anxiety disorders is attested by the partially "protective" effect of a network of acquaintances against the development of symptoms after the occurrence of life events. Conversely, patients with anxiety and depression tend to have defective social bonds with insufficient support from attachment figures and more time spent in unpleasant social interaction. In keeping with these findings, neurotic inpatients show less self-disclosure to others than do normals, and women with neurotic depression have few confidants (reviewed by Marks, 18).

Psychosocial and pharmacological factors can interact. Relevant to life events and social support systems in anxiety disorders are Leff's findings in chronic schizophrenics that high emotionality in the family predisposed the patient to relapse and that patients on phenothiazines could tolerate more life events before relapsing than patients on placebo. Appropriate medication thus raised the threshold at which breakdown occurred after environmental stress. Unfortunately, this protective effect of phenothiazines only seems to continue as long as the drug is given, and the relapse rate increases once again when the drug is withdrawn, even after several years.

This pattern of relapse on drug withdrawal regrettably also seems to be emerging with tricyclics given for phobias, rituals, and anxiety-depression. Unlike drugs, behavioral treatments produce lasting improvement in phobias and rituals, even after active psychological management ceases. In contrast, the drug effect in these cases seems to last only as long as the drug is given and to be significant only when the depressed mood is present to start with (reviewed by Marks, 18). When clomipramine was withdrawn after 8 months in ritualisers, there was a marked tendency to recurrence of pre-existing anxiety-depression, and in depressives, too, amitriptyline continues to have a protective effect into its second year. Whether tricyclics protect against the emergence

of anxiety-depression during life stress remains to be seen and would be interesting to examine. One is all too aware of the potential snags of long-term drug administration and also of accusations that drugs are being used to paper over cracks in society, but only longitudinal studies of the cost-effectiveness of drugs and psychological treatments in various anxiety disorders can inform us about the relevant tradeoffs. The time scale has to be over at least 3 years of followup, and simple ways of measuring life events and social supports are critical if the research is to have meaning.

FEASIBLE LONGITUDINAL EPIDEMIOLOGICAL STUDIES

Well-planned prospective longitudinal studies can yield much definitive evidence and answer several questions at the same time, including relationships between early personality and the development of subsequent syndromes, e.g., whether timidity predisposes to phobias and meticulousness to compulsive rituals.

There are many possibilities to consider for the prevention and management of anxiety disorders in children and adults, and the strategies and cost-effectiveness of each approach require careful examination. A tantalizing vista, for example, is that of general stress immunization of children which could be carried out both in schools and in the home. One would not envisage the education given in ancient Sparta but rather the application of certain principles.

Most people have trivial fears and rituals at some time or another, but, when these grow to invade their life space, the question inevitably arises as to whether the patients we see are those who fail to inhibit the growth of such minor phobias and rituals. Maybe we should not think in terms of why phobias and rituals are acquired in the first place, but rather why, once these are acquired, some persons should fail to extinguish them. This view resembles that prevalent about the spread of cancer. Cancer cells are regularly produced in the average organism, but they only spread when immunological and other defense systems fail. Maybe stress immunization could strengthen antibodies against stress, if given in the appropriate manner at the right time. The question is what is the appropriate manner, and what is the right time?

It is worth educating parents and teachers about the exposure principle of fear reduction which is so effective in behavioral psychotherapy. Perhaps children can be taught early to manage some of their own discomforts. One is reminded of the anecdotes about the childrearing practices of the Senoi who employed dream interpretation as a special form of exposure therapy at the breakfast table, so to speak. While it is possible to reduce anxiety about dental procedures and surgical operations, it is by no means clear how far improving such specific psychological areas leads to a more general tolerance of stress, and it is a long haul from that to producing a decrease in the incidence of anxiety disorders of various kinds, e.g., anxiety states and post-traumatic stress disorder.

Spinoff might ultimately come from behavioral treatments by exposure and anxiety management. These treatments produce lasting relief from phobias and rituals in most patients, but we cannot yet specify the critical features which separate the sensitizing exposure all such patients report they have had during acquisition of their pathology from the habituating exposure they undergo during therapy. Identification of the critical differentiating factors could help us not only refine the treatments by

eliminating redundant elements but also broaden applicability of the exposure approach to stress tolerance in general, i.e., develop the exposure paradigm into a wider and even more useful coping theory.

At the moment this seems far off, and specific stress immunization appears to be more realistic. It is easier to identify certain high-risk populations, to anticipate their problems, and to prevent them than to manage such problems after they have developed. There is already much work on methods to reduce separation anxiety in children admitted to hospitals. Children with dental anxiety and with school phobia can easily be identified and treated so that these problems are minimized. Widows at high risk for morbid grief after bereavement have been picked out and given bereavement counseling (22) which reduced their morbidity, compared to a control procedure.

Another strategy worth considering is identification of children who are social isolates at school in order to give them social-skills training at an early age so that they can develop the social contacts and support which might reduce later anxiety and depression. To lower the incidence of adult sexual dysfunction, we might consider widespread provision of early sexual education given in a matter-of-fact manner, including films of coitus, and counseling about the emotional as well as the physical problems of sex and love. Though such education might prevent much sexual anxiety, it is unlikely to make an impact on sexual deviation (paraphilia). An experiment in sexual education of this kind would require cooperation of education and parental institutions in those areas where such a vision would be socially acceptable. The work involved in a controlled study of this kind would be no greater than that in the successful studies of the prevention of cardiovascular disease in California towns (7). If an educational program began at age 10, a followup of 15 years would be needed before meaningful data about a reduction in sexual anxieties could be collected. The same long vista is needed for programs to reduce phobias, social anxieties and skills deficits, and depressive neurosis.

In health care as a whole, many advances have been made ahead of precise knowledge. Jenner's inoculation against smallpox, Semelweiss's measures against childbirth fever, and Snow's reduction of cholera in the Broad Street area resulted from actions taken before the exact etiological agents involved had been identified. They were short-term experiments which were highly successful, and we tend to forget the many that failed. The risk with longitudinal studies is that, when they are ineffective, failure takes long to be revealed. Nevertheless, informed guesses can be made about likely fruitful areas in which to start. We can already successfully treat several anxiety syndromes by behavioral means, even though the pathology is far advanced. Prevention of such pathology is a logical next step where it is possible to modify likely risk factors.

SUMMARY

Risk factors in anxiety disorders arise at many levels, as listed in table 2. Phyletic questions arise about the design characteristics of the species and its wiring diagram. There seem to be numerous "natural" fears and rituals, and maturational factors affect the times when they emerge. Organisms, including man, may have selective stimulus-response "valencies" or facilitatory connections. Some of these may be related to adult syndromes and need to be taken into account in programs of treatment and prevention.

At the genetic level, we might search for temperaments at risk for later morbidity, and multicenter research on MZ twins reared apart is mandatory to answer this in view of the small numbers available. The time is ripe to search for biological clocks which affect the acquisition and subsidence of various forms of anxiety, and such clocks would give a clue to the biochemical mechanisms involved.

Personality types might well relate to subsequent adult syndromes and point to ways of identifying high-risk individuals for prevention programs. In the psychosocial arena, appropriate aid at times of crisis is critical for prevention, as are more long-term protective social and pharmacological supports for vulnerable individuals.

There are many possibilities to consider for the prevention and management of anxiety disorders in children and adults. These need to be studied in regard to strategy and cost-effectiveness (table 3). General stress immunization is more difficult at present, but several specific programs are feasible for helping high-risk individuals in high-risk situations. For some, e.g., dealing with predictable stresses such as separation anxieties in hospital and in school, fears of dentistry and of surgery, bereavement, and sexual anxieties, short-term research over a year or two could yield benefits. For more long-term prevention, longitudinal studies are needed.

Table 2. Possible risk factors in anxiety disorders.

1.	PHYLETIC (design characteristics of species, wiring diagram)
	What are "natural" fears and rituals, and when do they develop?
	Can we map S-R valencies?
	Are these related to adult syndromes?
	Do they affect treatment and prevention?
2.	GENETIC
	Can we identify temperaments at risk for later morbidity?
	Possibility for multicenter research on MZ twins reared apart
3.	BIOCHEMICAL
	Do biological clocks affect acquisition and subsidence of anxiety?
	Do biochemical states affect acquisition and subsidence of anxiety?
4.	PERSONALITY TYPES
	Relationships to subsequent adult syndromes
	Identification of high-risk individuals for prevention
5.	PSYCHOSOCIAL AND ENVIRONMENTAL
	Aid at times of crisis
	Providing protective social networks of support
	Providing protective pharmacological support

Table 3. Possibilities for prevention and management

1.	General stress immunization and education, plus followup:
	Will this decrease anxiety states and post-traumatic stress disorders?
2.	Specific stress immunization:
	Identification of high-risk individuals and situations, management, and followup of their problems:
	Possibly applicable to separation, social, sexual, and dental anxieties, morbid grief, and social skills problems and isolation, phobias (dental, school, agoraphobia), depressive neurosis, sexual dysfunction.

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DISCUSSION

Dr. Hirschfeld: Do you have any personality data?

Dr. Marks: Regrettably, no. I was wondering to what extent some data might be gathered during the longitudinal schizophrenia studies which might shed light on the anxiety disorders. Can one ride on the back of some of these expensive studies?

Dr. Weissman: Do you have data on sociodemographic risk factors like age and sex for the different kinds of anxieties?

Dr. Marks: There are some interesting data there. For anxiety states and social anxieties, men and women do not seem to differ much, whereas most phobias predominate in women. Obsessive-compulsive disorders tend to be diagnosed equally by sex, but, in populations given behavioral treatment, women predominate. We wonder if this is because most behavioral treatment is given to compulsive ritualizers who avoid stimuli which evoke their rituals, i.e., to the more phobic-like compulsives, and phobic patients are usually women.

There are possibilities for identifying high-risk individuals which go back to the preparedness idea. It is possible that we have a continuum of sensitivity, let us say, to developing bradycardia to blood and injury stimuli, or to showing fear of heights. If we could identify those individuals who have low response thresholds on such dimensions, we might find that later such individuals, given subsequent stress episodes, are likely to develop relevant phobias, e.g., of blood or heights. We would need careful pilot studies first.

RISK FACTORS AND PERSONALITY DISORDERS

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IDENTIFYING THE DEPENDENT VARIABLES (THE DISORDERS)

To identify risk factors for personality disorders, the disorders themselves must be defined. Traditionally, personality disorders have occupied a special position in our psychiatric schema. Whereas other categories of disorder (i.e., psychotic, affective, neurotic, or organic) represent disruption of an individual's usual functioning in certain situations or at certain times, personality disorders represent "pervasive personality traits...exhibited in a wide range of...contexts...throughout most of adult life (1)."

This concept results in several problems. First, that of delineation. While there may be some trouble in identifying a decline or change in functioning of an individual, it is often more difficult to delineate the point at which a personality trait becomes an aberration. This is complicated by the fact that certain personality traits (e.g., some degree of compulsivity) may be adaptive in some situations.

Even when an individual's functioning is clearly maladaptive, and it can be agreed that some personality disorder is present, the definition and delineation of the disorder may still be a problem. Traits by which various personality disorders are characterized may appear during episodes of other psychiatric disorders (e.g., dependent interaction or vaguely paranoid ideation during an episode of a major depressive disorder).

Furthermore, there is the problem of distinguishing individual disorders among the general category of personality disorders. The early literature generally referred to personality disorders as "psychopathy." The inadequacy of this formulation, however, resulted in such breakdowns as hysterical, asthenic, or even paranoid psychopathy. Currently the idea of a fundamental disturbance underlying all personality disorders has been resurrected in some formulations of the borderline disorders. The deficiencies of this approach are confirmed, however, by attempts at further subdivision into "hysterical," "narcissistic," and "depressive-masochistic" types (17). With such difficulties in conceptualizing and describing personality disorders, it is no wonder that our knowledge of risk factors is limited.

DSM-III (1) has attempted to address these problems, first of all, by using a multi-axial framework. Thus, personality disorders are coded on Axis II, whereas the Clinical Psychiatric Syndromes are coded on Axis I. This should allow for retaining information regarding personality disorders even when they are overshadowed or distorted clinically by the presence of intervening clinical disturbances.

A further major characteristic of DSM-III is its use of specific, primarily descriptive, diagnostic criteria, for both inclusion and exclusion. Although not yet extensively validated and, in the case of the personality disorders, still relying largely on clinical judgement (such as whether or not there is a "restricted ability to express warm and tender emotions"), the DSM-III approach will make possible the testing of hypotheses regarding identifiable risk factors in more or less homogenous groups. Predisposing factors (risks) are presently not known, however, for most of the DSM-III personality disorders.

The DSM-III recognized nine disorders grouped into three clusters (table 1). This discussion starts with the disorders for which there are data available (Antisocial and Histrionic Personalities)[1] and then briefly reviews the disorders for which there are very few or no data.

Table 1. Personality disorders in the DSM-III.

1. "odd" cluster	2. "dramatic" cluster	3. "anxious" or "fearful" cluster
a. Paranoid	a. Histrionic	a. Avoidant
b. Introverted	b. Narcissistic	b. Dependent
c. Schizotypal	c. Antisocial	c. Compulsive
	d. Borderline	d. Passive-agressive

ANTISOCIAL PERSONALITY

Antisocial Personality (although referred to by a myriad of synonyms, including sociopath, psychopath, moral imbecile, **manie sans delire**, etc.) is a disorder long recognized and characterized by (according to the DSM-III) "continuous and chronic antisocial behavior in which the rights of others are violated (1)." Perhaps because of this feature, the disorder has been more thoroughly studied and delineated than many other personality disorders in which individuals simply remain quietly maladjusted.

Genetic Predisposition

A frequent theme in risk studies of Antisocial Personality has been the question of genetic effects. It has been the subject of numerous reviews, which should be consulted for details (12,32).

Among hypothesized genetic effects, the most straightforward, perhaps, is the effect of the Y chromosome. There is general agreement that Antisocial Personality is much more common among men. This sex difference has been consistently demonstrated across national, socioeconomic, and age lines, in ratios varying from four to eight men to one woman. In white North American men, the prevalence ranges from 2 to 6 percent, compared to from 0.5 to 1 percent in women (8).

Some explanations have been offered for this sex difference. Cloninger et al. posit a "multifactorial model" for the sex effect with a higher threshold necessary in women (8). Accordingly, multiple genetic and environmental factors contribute to the liability of developing Antisocial Personality, with female sociopaths a more deviant manifestation of the same etiological processes that are associated with the disorder in men. As evidence for this, significantly greater rates of Antisocial Personality have been found among relatives of sociopathic women than among relatives of sociopathic men (36 percent versus 17 percent among male relatives, 19 percent versus 4 percent among female relatives)(8).

An interesting corollary to the male preponderance among sociopaths is the suggestion that XYY karyotypes may be more common among violent criminals than the general population. After early reports that XYY males were more frequent in hospitals for the criminally insane, conflicting data have been gathered. Even assuming increased criminality among XYY men, such individuals account for a very small percentage of criminal men (a fraction of 1 percent) (19).

Robins found that having an antisocial or alcoholic father was a predictor, whether or not the father was also involved in rearing the child (28). As reviewed by Robins (29), findings in twin and adoptee studies have been consistent with some genetic predisposition. However, except for Robins (28), these authors based their diagnoses primarily upon criminality. Although perhaps about 80 percent of male criminals fulfill criteria for Antisocial Personality, there are exceptions, and it is also possible, though not common, to fulfill criteria for Antisocial Personality according to DSM-III, without criminality (15).

The possibly biased selective placement of adoptees raises another concern. As pointed out by Hutchings and Mednick (18), the social class of biological and adoptive fathers was correlated in some of the European studies, suggesting that genetic and environmental influences may not have been entirely separated. This probably resulted from attempts by social agencies to match adoptees and adopting families on a number of variables, including socioeconomic status. Furthermore, United States agencies are known to match on the basis of race and ethnicity, leading to additional biasing.

Despite these possible problems, the preponderance of evidence favors some hereditary predisposition to Antisocial Personality.

Biological Factors

Whatever the hereditary predisposition, the nature of the biological factors transmitted is not yet known. Investigators have attempted to delineate such possible biological factors. Research thus far has identified, insofar as possible, differences in EEG's, in autonomic arousal, and in learning. These studies were reviewed extensively by Hare (16) and, more selectively, by Cloninger (6).

As Hare points out, EEG studies, although subject to several methodological shortcomings, have often demonstrated an increased prevalence of slow-wave activity (particularly temporal), as well as a positive-spike phenomenon. The slow-wave activity resembles that found in children, thereby suggesting "cortical immaturity." It is an appealing generalization, considering the egocentricity, impulsivity, and inability to delay gratification common to some children and certain sociopaths. The positive-spike phenomenon has been associated to some degree with episodes of trivially provoked, unrestrained, violent, destructive, yet coordinated and well-directed, behavior.

A further hypothesis, one that may tie cortical functioning to other factors, is the concept of low cortical excitability or low cortical arousal. Evidence for this comes from a variety of experimental indices, including slow cortical recovery from successive stimulation and a lower threshold to sedation (or paradoxical excitation) from depressant drugs (e.g., alcohol, barbiturates). It has been suggested that low cortical arousal could, perhaps, account for the stimulation-seeking, monotony-intolerant behaviors observed among many sociopaths. To escape the putative dysphoria associated with low cortical activity, the individual seeks out highly stimulating (although perhaps ill-considered or ultimately harmful) experiences in order to achieve a more optimal level of arousal (6).

Low cortical arousal appears to be related in a reciprocal manner to high somatic anxiety and high levels of muscle tension, this interaction hypothesized as mediated via the reticular system and the frontal cortex. Low cortical alertness is associated with a lack of inhibitory control over the autonomic and musculoskeletal systems. Sociopaths have, in fact, been reported to have lower psychic anxiety, although higher somatic anxiety and muscle tension, than normals. Somatic anxiety and muscle tension have been reported to be positively correlated with impulsivity, and psychic anxiety to be inversely related to extraversion.

These findings must be interpreted with caution, however. As Cloninger (6) points out, any unitary conception of arousal is inadequate. It is not clear, for example, that a particular arousal level is an underlying trait of the individual. Relaxation training has been shown to affect the response to repetitive stimulation as measured by skin conductance, so that the state of relaxation may be a confounding variable (31). Furthermore, even if distinct psychophysiological and even EEG differences were consistently identified in sociopaths, these factors might still be the results of, or at least highly modified by, conditioning and learning.

Another posited risk factor involves a learning deficit. As developed by Eysenck (10) and reviewed by Hare (16), the sociopath is an extrovert and has a nervous system predisposed to the rapid development of cortical inhibitory potentials, and as a result conditioned responses are acquired slowly and extinguished rapidly. Thus, the sociopath would more likely be inadequately socialized, especially in terms of fear- or anxiety-mediated responses. Evidence, here, is certainly preliminary, and any conclusions are clearly tentative, but the findings do fit the observation that many sociopaths fail to modify behavior despite anticipating noxious consequences.

Psychodynamic Factors

Numerous psychodynamic formulations for the etiology of Antisocial Personality have been suggested and are reviewed by Rappeport (26). These include unresolved oedipal conflict, pregenital fixation, acting-out to deal with inner conflict, unconscious parental encouragement of antisocial behavior, or serious ego or superego defects. As

pointed out by Robins, however, such conceptualizations are inferential and not demonstrable and are often simply convenient summaries rather than a more profound analysis of observable behavior (27). Until it can be demonstrated that such constructs can be reliably ascertained, their usefulness cannot be tested.

Socioenvironmental Factors

Even the most biologically oriented investigators recognize the importance of these factors in at least modifying the underlying disorder in sociopathy (6,16,29). Either-or hypotheses concerning the effects of biological or environmental factors on the etiology of sociopathy are clearly oversimplified. Except in the case of adoption, the same individuals who provide the genetic endowment also provide parenting and do much to determine the early home environment that appears to be important in the development of sociopathy. Thus, early environmental factors that correlate with the development of sociopathy (parental loss, emotional deprivation, parental rejection, inconsistent disciplinary techniques, etc.) are themselves correlated with the genotype.

These early familial environmental factors cannot be the whole story, however, in light of the adoption studies reviewed above in which sociopathy (or criminality) occurred in adopted-away offspring of sociopaths (or criminals) at greater than expected frequency. The occurrence of sociopathy in environments conducive to (as Cleckley states) "happy development and excellent adjustment" (5) again argues against a simple home environment model.

Other social-environmental factors that have been associated with the risk of sociopathy are: being a member of a minority or disadvantaged racial group, living in an urban rather than rural setting, and having low socioeconomic status (23). The causative mechanisms here, however, are undoubtedly complex and interactive with biological and home environment factors and can only be speculated upon at present. Race, however, appears more related to criminality than sociopathy per se. As Cloninger et al. point out, there is no evidence of a difference in the prevalence or transmission of sociopathy according to race (8).

Childhood behavioral patterns also have been shown to predict future sociopathy. Robins reported that approximately 40 percent of childhood delinquents continued such behaviors into their twenties and warranted a diagnosis of Antisocial Personality (28). Furthermore, there was a positive relationship between the number and earlier onset of delinquency symptoms and the likelihood of sociopathy. According to DSM-III terminology, most delinquents would fall into the category of "Conduct Disorder of Childhood or Adolescence."

Related to this are hyperkinetic child syndromes known in the DSM-III as "Attention Deficit Disorders with or without Hyperactivity." These syndromes have been reported to predispose to delinquency (i.e., conduct disorders) in adolescence and sociopathy in adulthood. Interestingly, some criteria for the Attention Deficit Disorders emphasize hyperactivity, impulsivity, and distractability—traits posited as underlying traits in the Antisocial Personality. Recent authors have emphasized, however, that only the hyperkinetic children with delinquent behavior are at risk for sociopathy (25).

HISTRIONIC PERSONALITY

Histrionic Personality is another in the "dramatic" cluster of DSM-III personality disorders. Some data exist regarding risk factors relative to it, but conclusions must be very tentative because of long-standing diagnostic confusion. The Histrionic Personality of DSM-III overlaps the traditional categories referred to as hysterical personality, hysterical neurosis, conversion neurosis, dissociative neurosis, hysteria, Briquet's syndrome, etc. As reviewed by Cloninger (6), Briquet's disorder and Histrionic Personality are highly correlated. Kimble reported that 90 percent of adult histrionics had Briquet's syndrome (20). Conversely, approximately two-thirds of Briquet's syndrome patients also show prominent histrionic traits (6). Thus, certain generalizations can be tentatively made regarding Histrionic Personality.

Only 10 to 25 percent of patients with conversion symptoms (including dissociative phenomena) have either a Histrionic Personality or Briquet's disorder (6). This may account for the conclusions of observers such as Slater (34) who stated "the hypothesis of a genetical basis...has had to be discarded." He based his conclusions on studies in which patients were included under the rubric of hysteria on the basis of conversion symptoms alone.

Histrionic Personality, as defined by DSM-III, is not diagnosed on the basis of unexplained complaints suggesting somatic disease, as are the Somatoform and Dissociative Disorders. It is defined, instead, on the basis of a pattern of behavior that is essentially "overly reactive, intensely expressed, and perceived by others as shallow, superficial, or insincere" and associated with "characteristically disturbed interpersonal relationships" and "poor sexual adjustment (1)."

DSM-III notes that men with this personality may come into conflict with the law, suggesting an association with Antisocial Personality. Furthermore, these individuals "crave excitement" (similar to stimulation-seeking) and show "a limited capacity for sustained intellectual achievement" (similar to distractability) suggesting again that there is behavioral overlap with Antisocial Personality. The possible relationship between Histrionic and Antisocial Personalities was reviewed by Temoshak et al. (35) and developed more explicitly by Cloninger (9). The apparently greater frequency of Histrionic Personality among women than among men is similar to the sex distribution of Briquet's syndrome, but just the opposite of the sex distribution of Antisocial Personality (5). Cloninger and Guze (7) suggest that "depending on the sex of the individual, the same etiologic and pathogenic factors may lead to different, though sometimes overlapping, clinical pictures." Thus, much of the discussion of Antisocial Personality may also be applicable to Histrionic Personality.

Genetic Predispositon

No genetic studies of Histrionic Personality per se have been carried out. Because of the overlap between it and Briquet's syndrome and Antisocial Personality, however, it may be reasonable to infer that there is some genetic predispositon for Histrionic Personality, in that such a predisposition has been demonstrated for both of the other disorders.

Biological Factors

Again, biological studies of individuals with Histrionic Personality as defined in DSM-III have not been carried out, but much of what has been said regarding biological differentiation of sociopathy probably can be applied to Briquet's disorder and Histrionic Personality as well. Eysenck, in fact, lumps hysterics and sociopaths as "hysterical psychopaths," a term that is used frequently in Great Britain. Patients with "hysterical personality" have been found to have a lower sedation threshold than normals (4, 33), again suggesting low CNS arousal. On some parameters (e.g., autonomic variability) however, histrionics and sociopaths appear to be at opposite ends of a continuum, with sociopaths showing high and histrionics low variability (16). These studies deliberately selected sociopaths with low manifest anxiety, however, and they failed to account for state differences (the sociopaths were generally in a state of relative quiescence, whereas the hysterics were acutely distressed).

There is the suggestion that conversion and dissociative reactions (apparently more common both among histrionics and sociopaths than in the general population) may be triggered by high cortical arousal. The hypothesis is that persons who normally have lower levels of arousal may develop strong reactive inhibition when strongly aroused, thereby inhibiting sensory input (16).

Psychodynamic Factors

Much has been written on presumed underlying psychodynamic patterns of the Histrionic Personality. For such formulations to be relevant to a discussion of risk factors, however, specific psychodynamic patterns would need to be consistently detectable in Histrionic Personalities and be recognizable **prior** to the full development of the personality. To date, such evidence has not become available.

On the other hand, as reviewed by Chodoff (3), there may be consensus among psychoanalysts that a particular pattern of family dynamics is responsible for the Histrionic Personality. A young girl deprived of adequate mothering turns to, or is seduced into, an abnormally close relationship with her father. This relationship becomes "sexualized," and she learns to use sexually inviting manuevers to earn dependency gratification from future father figures. Chodoff points out that this hypothesis only fits some histrionics and was not fully supported at least by one survey. Blinder, however, found that 17 of 21 hysterical women (most of whom were presumably histrionic) described their parents as "cold, ungiving, remote, and quarrelsome" (2). Other investigators reported that parental disharmony and/or neglect of the child as long as it was not in acute distress or physically ill characterized families of Hysterical Personalities. The degree to which these reports may have represented retrospective distortion by the patients cannot be determined; prospective studies are clearly needed before such experiences can be evaluated as possible risk factors.

Socioeconomic Factors

Studies have generally shown that hysterics (and hence many histrionics) come from home environments similar to those associated with the development of sociopathy (6). Factors characterizing these home environments include low socioeconomic status, loss of one or both parents, living in foster homes or orphanages, or simply not being raised entirely in the parental home. The report of Luisada et al. is perhaps the only study relevant to possible risk factors for Histrionic Personality in men (22). They found

that 27 men with hysterical personalities "usually described their fathers as unassertive or absent during their early childhood." Among the index cases, the "vast majority" were heterosexual, but "all" had disturbed sexual relationships. Effeminacy was observed in 4 of the 27 men as well. However, since the sample included only hospitalized cases, the data were obtained by record review rather than by systematic interview, and most of the findings were reported in approximate terms rather than actual proportions, the report can only be considered suggestive. The discussant of the Luisada paper (M.S. Breslin) notes that Western culture encourages and tolerates hysterical behavior in women, whereas Eastern culture does the same for men. No empirical evidence was volunteered for this observation, however.

DISORDERS FOR WHICH THERE ARE FEW OR NO DATA

Few investigations have been reported concerning possible risk factors in other personality disorders. Thus far, very little in the way of systematic validation of the many proposed biological, socioenvironmental, psychodynamic, or psychological formulations is available. In fact, attempts to define and validate these disorders are only now beginning.

Much has been written about possible associations between various personality disorders and the DSM-III clinical syndromes. Personality disorders in the "odd" cluster (Paranoid, Introverted, and Schizotypal), for example, have been linked to clinical Schizophrenia. A relationship between Compulsive Personality Disorder and the clinical syndrome of Obsessive Compulsive Disorder seems reasonable, and Kringlen (21) has reported that 72 percent of patients with Obsessive Compulsive Disorder also have a compulsive personality premorbidly. As Flor-Henry (12) points out, however, other investigators have not found such a relationship. Thus, care must be taken that data applying to the clinical syndrome, such as Flor-Henry's report of left dominant frontal dysfunction (13), not be uncritically generalized to a related personality disorder.

RECOMMENDATIONS FOR FUTURE RESEARCH

Identifying the Disorders (the Dependent Variables)

It is useless to try to identify risk factors for a presumed personality disorder until the disorder can be reliably identified and its validity established. This principle has not been consistently followed. Even with Antisocial Personality, where there has been perhaps the best agreement as to what constitutes the disorder, criteria have varied from study to study, sometimes making it difficult to generalize from one study to another.

DSM-III is a major step in the right direction. Although disagreement may exist with regard to the inclusion of specific disorders and the criteria for each, a common framework has been proposed for investigators to follow and, with focused research, improve upon.

A rationale for explicit diagnostic criteria has been presented elsewhere (11), but several problems exist in studying personality disorders. Personality disorders represent "pervasive, maladaptive lifestyles," that need not be associated with subjective distress

in the individual (1). Thus, an individual with a personality disorder may not present for treatment with a complaint directly related to the personality disorder. Instead, psychiatric contact may result from an intercurrent clinical psychiatric syndrome (e.g., a Major Depressive Disorder or Substance Use Disorder), or problems with society (e.g., criminal behavior or employment incapacitation). Risk factor research based primarily or only on such cases, however, could be biased. Individuals with such complications could be overrepresented and the sample not necessarily representative of all individuals with the particular personality disorder.

Adequate sampling techniques are thus very important. It may be necessary to carry out general population surveys. Such studies using explicit diagnostic criteria have not yet been reported with regard to personality disorders. Previous population surveys either lacked adequate diagnostic criteria for the personality disorders or have used vaguely or idiosyncratically defined disorders and criteria. Even current general population surveys (Epidemiologic Catchment Area studies) using the NIMH Diagnostic Interview Schedule (DIS) (30) do not include items to assess many of the DSM-III personality disorders.

Adequate assessment of the personality disorders presents many problems. Except for disorders such as Antisocial Personality, in which the presence or absence of explicit behaviors (e.g., excessive truancy, repeated physical fights, etc.) can be independently confirmed, it is uncertain to what extent self-report by a subject is entirely satisfactory. To qualify for a Passive-Aggressive Personality Disorder, for example, the individual must show "resistance not expressed directly but rather through at least two of the following: (1) procrastination; (2) dawdling; (3) stubborness; (4) intentional inefficiency; (5) forgetfulness." In studies at Washington University, attempting to assess such behaviors by supplementing a systematic interview (15) with additional self-report questions, it has been found that many individuals suspected of using such mechanisms deny them categorically. Vaillant, on the other hand, has suggested a way of assessing various defense mechanisms, but this work needs further evaluation (36). Many sources of information may be needed, then, to evaluate some traits associated with the putative personality disorders.

Though educational, correctional, and medical records have been demonstrated to be diagnostically useful for some personality disorders, such as Antisocial Personality (24), they may not be helpful for more subtle disorders, such as Introverted, Narcissistic, Avoidant, or Dependent Personalities, where the essential aberrations may not appear as overt behaviors but as underlying attitudes. On the other hand, interviewing family members, friends, employers, and other associates may be more useful. This may pose other problems, however, related to consent, confidentiality, and disagreements among various informants. Despite these complexities, information about an individual's lifestyle must be sought if we are to expect personality disorders to achieve significant validity.

Given the above information, the problem of integrating the various sources of information into a personality diagnosis remains. To be of practical usefulness, such diagnoses should be straightforward and consistently reproducible. Thus, the statement regarding Borderline Personality organization, that "the definite diagnosis depends on characteristic ego pathology and not on descriptive symptoms" probably precludes such consistency because "ego weakness" is described in such an abstract and circular way: "predominance of primitive mechanisms of defense characteristic of the borderline

personality organization" and "lack of differentiation of self and object images (17)." It has not been demonstrated that even highly trained observers can reliably evaluate such constructs.

Separating and distinguishing one personality disorder from another is an important element in establishing the reliability and validity of any personality diagnosis. The Borderline Personality, for example, overlaps extensively with other disorders. It has not yet been demonstrated that there is something more "fundamental" about the Borderline Personality to "explain" the overlapping features. Thus, the usefulness of the concept remains questionable.

Finally, before committing the time, money, and effort necessary to carry out well-designed risk factor studies, it should be demonstrated that a proposed Personality Disorder has predictive value in terms of lifestyle, life course, complications, or response to treatment.

Assessment of the Risk Factors (the Independent Variables)

Evaluation of any but the most simple risk factors is very difficult. Interview of the proband, even using a structured instrument by a trained interviewer, may not be adequate. Studies such as that of Gunderson (14) who interviewed borderline patients regarding their families can only be considered suggestive. He concluded that the families showed "a pattern of parental neglect distinguished by rigid tightness of the marital bond to the exclusion of the children." This conclusion may be the result of distortion by the interviewed subject, however. It is impossible to judge whether the reporting of such a familial pattern reflects actual parental attitudes or perceptual bias on the part of the subject. Resolution of this question probably requires careful interviewing of multiple family members if not actual in-home observations.

An additional problem with retrospective studies is the difficulty in distinguishing the cause (i.e., a risk factor) of a disorder from its consequences (i.e., complications). With certain risk factors (age, sex, **parental** socioeconomic class, or **parental** psychiatric diagnoses), this is fairly straightforward. These variables have been evaluated relative to certain personality disorders. Other variables, however (e.g., the **individual's** socioeconomic class, marital status, physical health, etc.), may be less straightforward and necessitate careful examination of any causal conclusions. For example, the greater prevalence of schizophrenia among lower socioeconomic groups may indicate that such status is a risk factor for schizophrenia, but, as many investigators have noted, this association is more likely to be a consequence of the illness rather than a cause. Similar arguments may be pertinent in discussions of the relationship between sociopathy and low socioeconomic status.

Despite these difficulties, there is reason to be optimistic that improved description and validation of personality disorders is possible.

NOTE

1. We capitalize diagnostic labels that correspond to categories defined in DSM-III, following the DSM-III convention.

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DISCUSSION

Dr. Regier: Dr. Guze has raised some important methodological issues that are inherent in chronic disease epidemiology, for example, the whole issue of the latency period between the introduction of a cause and the observation of an illness. Some of the issues he raised will be taken up by the speakers on life stress because they apply to all the disorders.

III

THE INDEPENDENT VARIABLES:

SOME BROAD RISK FACTORS

The papers which follow have a two-fold purpose. First, to review the risk factors that were discussed in connection with specific major mental disorders. Second, to bring in as dependent variables mental disorders other than the major ones by examining the general effects of sociodemographic variables, life stress, family history, and psychophysiological factors as independent variables.

DEMOGRAPHIC AND SOCIAL-ECOLOGIC RISK FACTORS FOR MENTAL DISORDERS

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INTRODUCTION

A **risk factor** is defined here as any characteristic associated with increased probability of becoming mentally disordered. In this definition, "risk" does not necessarily imply that the factor causes the disorder nor that intervention or prevention is possible. A **causal factor** is a risk factor that is known to have a causal effect on the disorder under study. An **efficient cause** is defined here as a risk factor which is a necessary cause of the disorder in a large enough proportion of cases to make intervention worthwhile. The notion of efficient causes implies neither absolute necessity nor sufficiency in onference, it seems to me, is to locate risk factors and try to judge which among them are causal factors and which are most likely candidates as efficient causes.

For what follows I have reviewed social epidemiologic research relevant to risk factors for mental disorders which are related to demography and ecology. My aim is to summarize all such research conducted in the world to date, excluding only those studies that are methodologically inferior. Studies relying on treatment facilities for casefinding are considered methodologically inferior, except for the diagnosis of schizophrenia and sometimes other psychoses. Such a comprehensive review is made possible by the many excellent reviews already available, on which I relied very heavily. The summary of results is portrayed in table 1.

IMMUTABLE DEMOGRAPHIC CHARACTERISTICS: SEX, AGE, AND ETHNIC STATUS

Some demographic characteristics are unchangeable. Their immutability has an advantage and a disadvantage for us. On the plus side, once an association is established between one of these factors and risk for mental disorder, there need be no concern that the mental disorder may cause the demographic factor; any causal relation is in the other direction. This advantage does not exist for most demographic factors. The disadvantage of the immutability is that intervention is impractical.

Table 1. Relative risks for demographic variables.

Demographic Variables	Specific Disorders					
	Schizophrenia	Bipolar Affective	Unipolar Affective	Mild Depression	Anxiety	Antisocial
Sex	1.0	1.5	2.0	2.0	*	5.0
Age	2.0	?	?	?	?	---
Ethnic Status	2.0	2.0	2.0	2.0	2?	4.0
Class	10.0	?	1.0	2.0	1?	5.0
Employment	9?	*	*	2.0	?	2.0
Residence	1.0	1.5	*	1.5	*	3.0
Marital Status	4.0	2.0	2.0	1.5	?	2.0

--- = Not appropriate
* = No data
? = Data ambiguous

NOTE: The increase in risk for mental disorder for persons having the risk factor is given in the table, if there are sufficient data to support this level of accuracy. Often several studies yield approximately the same risk ratio, but in other cells the risk ratio is based on a single study. Where there are varied estimates of risk ratio all within a limited range and all in the same direction, the high estimates are reported: Where a "1" is entered in the table, there is repeated evidence of no relationship. An asterisk indicates that reasonably good data could not be located; a question mark indicates that the data are contradictory or indirect. For the three ecologic variables, there is insufficient consensus in measurement to yield definitive high-risk groups. All entries in table 1 are intended to portray the simple one-way relationship, with other variables not controlled.

Males and females differ in susceptibility to mental disorder: For schizophrenia there is probably no relationship to sex (25); for affective disorder, especially depression, the male-to-female ratio is about 1:2 (2). For the anxiety disorders there are no data from field studies, partly due to the newness of the diagnosis, although it is usually reported to be more common in women. For antisocial personality disorder, males predominate by a factor of 5:1 (31). Table 1 displays these relative risks.

The relative risks for age have been estimated here by comparing high- to low-age groups within the adult range of 21-65 years. For schizophrenia there is a steep rise in incidence in young adulthood, with a peak at about 30 for males and 35 for females (11). For affective disorders the data are ambiguous, though there is some evidence for a peak incidence in females at around the age of 40 (2). The interpretation of age data in the affective disorders is clouded by the difficulties of controlling for marital status, which affects the risk materially (see below); the relationship is certainly not as strong as for schizophrenia. The anxiety disorders are commonly reported to be more frequent in childhood and adolescence, but data are few (1). Antisocial personality disorder and other diagnoses on Axis II in the new Diagnostic Manual are assumed to be lifelong behavior patterns without a definable age of onset.

Ethnic status is an easily identifiable characteristic which implies a particular cultural history shared with others. Race, national background, religion, and language are the most common ethnic identifiers, but there are many others. Each mental disorder is associated with some ethnic groups which are at higher risk than others, but this is difficult to summarize because there are many distinct ethnic groups and many ethnic classifications. There is evidence that Irish, Croats, Russians, and native-born Israelis have higher risk for schizophrenia (a factor of two or so: 26, 27); that Ashkenazic Jews have higher risk for affective disorder (17,19); that American blacks have higher risk for antisocial personality disorders (32); and so forth. But there are severe problems in interpreting the data, since there is not yet an acceptable methodology, combining uniform casefinding and case-identification, in cross-cultural psychiatric epidemiologic research.

SOCIAL CLASS, EMPLOYMENT, RESIDENCE, AND MARITAL STATUS

In epidemiologic research, changeable demographic characteristics pose the problem, noted above, that they can be either a consequence or a cause of mental disorder. The line of reasoning that mental disorder results from a demographic characteristic—for example, lower class status—is called the causation argument; the line of reasoning that mentally disordered persons select themselves into certain demographic statuses is called the selection argument; and the whole issue is termed the causation-selection issue (6,28).

Social class is the ranking of an individual as to his access to resources in his society. The most common indicators of social class are the occupational prestige score, years of education, and income. The availability of three different indicators exacerbates the problem of interpretation, discussed below, even if the causation-selection issue is resolved.

The inverse relationship of risk for mental disorder to social class is one of the most consistent findings in the field of psychiatric epidemiology, equaled only by the relationship to marital status. For schizophrenia, in five of the seven community studies

(6) and 15 of the 17 treated-case studies, the lowest class had the highest rate of disorder (11). The relative risk ran from about 3 to 1 in some studies to 10 to 1 in others for the lowest class as compared with the highest, as shown in table 1. The causation-selection issue with regard to social class and schizophrenia is still unresolved, but there is strong indirect evidence that the relationship is explained by selection. This evidence includes the relatively high heritability of schizophrenia and the insidious and disabling course of the disorder. In 11 studies of class mobility of schizophrenics, 7 reported downward mobility, and the other 4 reported no relationship of schizophrenia to class mobility or had ambiguous results (17). The rate of downward mobility among schizophrenics is sufficient to explain the size of the class differential (13).

The relationship of affective disorders to social class is complex, as indicated in table 1. For bipolar affective disorder, there is most probably no relationship at all. For minor depression and depressive mood, there is a moderately strong inverse relationship, with the lowest class having a higher risk by a ratio of about 2 to 1 (2). For major depressive disorders, the findings are contradictory and unclear, in part because the diagnosis is newer than others. I suspect there is little or no relationship for risk of anxiety disorders to social class. Risk for the DSM-II diagnosis of neurosis (the closest thing to anxiety disorder) was highest in the lowest class in only 6 out of 13 available studies, and there was no clear pattern in the other 7 studies (6).

For the diagnosis of antisocial personality disorder, there are very few studies, but they unambiguously reveal higher risk among the lower class with about a 5 to 1 risk ratio of lower to upper class (32).

Employment status is defined here as a simple dichotomous variable indicating whether a person is presently in the work force or not. Among those not employed, there are important distinctions, such as whether one is a student, retired, disabled, not in the labor force but working to maintain a household, and unemployed and looking for work; but I mean to ignore these distinctions to simplify the discussion and to concentrate on the dichotomy. The vast majority of adults in the age span of 25-65 are not students, disabled, or retired.

There is convincing evidence, from many independent and diverse longitudinal studies of aggregate-level time-series statistics dating from Durkheim, that a change in the rate of employment in a given area is associated with a change in the rate of admission to mental hospitals and in the rate of suicide in that area (9). Since admissions to mental hospitals are dominated by schizophrenics, and suicides by affective disorders, this relationship associates the two major mental disorders with loss of employment. The relationship is very strong on the aggregate level, but it is not possible to estimate relative risk with these data, and it is even possible that no relationship exists at all on the individual level.

There are very few studies on the effects of unemployment on individuals. Table 2 presents some recent data on employment status and high scores on the Center for Epidemiologic Studies Depression (CES-D) Scale (16).

The "other" category is almost totally comprised of the unemployed or laid-off. The risk is about twice as high as for those working—28 percent with high scores versus 13 percent. Since these data are cross-sectional, they could easily have resulted from the selection of persons prone to depression into the ranks of the unemployed. Fortunately, there are three sets of longitudinal data on this question. Two of these analyses are from the major real-time longitudinal studies of occupational histories

conducted at Ohio State University and the University of Michigan (4,29). Both reveal a causal effect of becoming unemployed on measures related to depression. The third study was designed specifically to test the hypothesis that becoming unemployed affected the risk for depression, but it failed to show any effect (19,23). One is tempted to set aside the one contradictory study as methodologically inferior or as having a strange sample, but more research can be anticipated in this important area.

Table 2. High CES-D Scores by employment status (16).

	CES-D Scores Above 16	
	Percent	N
Working	13	1,608
Keeping House	21	934
Student or Retired	15	176
Other	28	149

There are very few data on the effects of unemployment on other disorders. If one accepts data from followup studies that about one-third of schizophrenics are unable to work, that is about six times the average rate of unemployment in our economy; combined with a 1 percent prevalence of schizophrenia, the relative risk for the unemployed can be indirectly estimated at about 9 to 1 (33). For antisocial personality disorder, data from the only available study indicate the risk of having this disorder is twice as high among the unemployed, but unstable occupational history is one of the diagnostic criteria (31).

For the purpose of this presentation, the variable, **residence**, is defined in terms of the absolute size of the place in which an individual lives. The strongest comparisons have been made between "rural" areas—in open country or in villages of less than 2,500 residents—to "cities"—usually large metropolitan areas with greater than 100,000 persons. The findings are summarized in table 1. For schizophrenics, the relative risk is about three to one in treated case data (11) but roughly equivalent in field studies (7). For affective disorders, there is little information, but the best guess is that bipolar affective disorder occurs slightly more frequently in rural areas (14) and mild depression more often in cities. For anxiety disorders, there are no directly relevant data, but the consistent finding of higher rates of neurosis in urban areas, according to the old diagnostic system, suggests a higher risk for anxiety disorder in cities (7). Antisocial personality disorder is much more frequent in the city, by a ratio of 3 to 1 (7).

The remaining changeable demographic variable, **marital status**, is strongly related to the mental disorders. Schizophrenics tend not to be married, and the risk of

unmarried persons being schizophrenic is about four times that of the married. Table 3 lists relevant studies published after 1945, comparing the ratios of risk for all categories of nonmarried, together, with the risk for the married (12). Considering the diversity of time and place these studies represent, the consistent risk ratio of about four is fairly impressive. All the affective disorders tend to occur more often to not-married individuals (2). There are no data for anxiety disorders. Individuals with antisocial personality disorders are much more likely not to be presently married, but this characteristic, again, is tied into the diagnosis (31).

Table 3. Summary of studies of marital status and schizophrenia. Ratios of rates of schizophrenia, single to married. Adapted from Eaton, 1975(12), where the references are given.

Author and Date	Male	Female	Total
Odegaard 1946	4.7	3.0	
Odegaard 1953	4.3	3.7	
Norris 1956	6.2	3.7	
Thomas and Locke 1963			
New York	4.0	3.3	
Ohio	6.7	3.4	
Malzberg 1964			4.28
Stein and Susser 1970	7.2	2.6	
Eaton 1975			3.41

THE ROLE OF INTERVENING VARIABLES

The variables connected to ecology have a different status in risk research than do the demographic variables. First, since they cannot be dichotomized in a reasonable way, it is impossible to state relative risk, and so they have not been included in table 1. Also, the lack of consensus on measurement of these variables presents problems for the estimation of risk. Finally, the ecological variables to be considered—social support, community integration, and crowding—can be hypothesized as intervening between some of the demographic variables discussed above and risk for disorder. A brief discussion of the whole spectrum of intervening variables, including these three ecological factors, is appropriate at this point. Table 4 presents the relationship of the demographic variables we have considered to these intervening variables.

Table 4. Relationship of demographic variables to hypothesized causal factors.

Hypothesized Causal Factors	Demographic Variables						
	Sex	Age	Ethnic	Class	Employment Status	Residence	Marital Status
Genetic factors	X	X	X				
Material resources	X	X	X	X	X		
Culture-socialization	X	X	X	X		X	
Natal care			X	X		X	
Stress	X	X	X	X	X	X	X
Social networks	X	X	X	X	X	X	X
Community integration			X			X	
Density				X		X	

The intervening variables named "hypothesized causal factors" are very gross; most of them involve entire disciplines of research. If we were to decide that one of these intervening factors was uniquely responsible for a mental disorder, it might require generations of research to understand the causal factor well enough to design an intervention. A "X" has been placed in table 4 when there is empirical evidence or relatively uncomplicated logic suggesting a relationship between the demographic variable and the causal factor in a direction that could explain the risk as stated in table 1.

Material resources include power and wealth. Females, young persons, certain ethnic groups, the lower class, and unemployed persons are disadvantaged in our society and have less access to these resources. This factor may operate in concert with stress, in that inability to locate these resources may cause mental disorder only when an unexpected situation—a stress—presents itself.

Culture and socialization include all those factors associated with lifestyle and upbringing that lead to relatively permanent personality differences among groups. They include things like cognitive rigidity, expectation of external control, helplessness-hopelessness, coping style, and so forth. Again, many researchers feel this sort of factor works in concert with stress.

Inadequate natal care is a potential causal factor for all the mental disorders. Some ethnic groups, the lower classes, and rural areas get much poorer care of this sort than others, and the differences—as measured by perinatal mortality, for example—are of sufficient size to explain the magnitudes of risk for these demographic variables.

Stress is defined here as a personal situation where expected performance exceeds estimated capabilities. Unexpected situations of various kinds are the most common types of stressors. Since there is another presentation on stress in this volume (8), I will not discuss it here, except to note that stress could serve as an intervening variable for every single one of the demographic variables.

ECOLOGICAL FACTORS: SOCIAL SUPPORTS, COMMUNITY INTEGRATION, AND CROWDING

These three ecological variables could each conceivably intervene in the causal chain between the possession of the demographic statuses listed in table 4 and the occurrence of mental disorder. Social networks provide a potential explanation for every single demographic factor. Community integration could explain relationships between risk for mental disorders and either ethnic group or area of residence. Density could explain a relationship of the occurrence of mental disorders to social class or, obviously, to area of residence.

The idea that certain types of social relations are protective against mental disorders and, in particular, that social isolation is harmful to one's mental health, has been around for a long time (10). The notion of "social supports" connotes the protective aspect, but it is also true that social relations can be harmful to one's mental health. The study of the effects of social supports in mental health is currently very intensive among dozens of investigators, probably because of the need to maintain schizophrenics in the community in the wake of the community-care movement, but perhaps also because of the developing quantitative methods for conceptualizing and measuring social

networks (3,5,21,22). Unfortunately, there is no consensus in this field about how to measure and conceptualize social supports. There are, however, several issues concerning supports that we should consider.

One issue is whether to study social supports or social networks. A social network is the sum of the sociometric linkages of the individual, without regard to the quality of the links. An advantage of studying social networks is that they lend themselves to relatively objective measurement, and the measures are not necessarily contaminated when a measure of mental status is obtained simultaneously.

An alternative is to study the supportive quality of relationships an individual engages in, which I term "social supports." Here the measurement is much more difficult because one must either rely on the perceptions of the supportive quality of the relationships, as reported by the individual and those around him, or use behavioral measures. Perceptual measures are easily contaminated by the mental status of the individual, and behavioral measures are extremely time-consuming.

Another issue concerns the extent of the social networks one should study. One can study networks of close friends and relatives, usually called "primary networks." Extended networks include voluntary group associations, such as recreational, religious, and professional associations. Finally, one can study networks at the level of the geographically defined community. "Community integration" in table 4 refers to the density of the network at the level of the group large enough to support itself—in a rural area this could be a town or village, but in most western countries the definition requires a city.

There is strong evidence that the primary social network of mentally disordered persons is much smaller than that of the general population and different in other ways. It is not clear whether this difference causes mental disorder, but it seems almost certain that mental disorders of certain kinds change a person's social network. Evidence that social networks are a causal factor for mental disorders comes from several prospective studies. In one study, several network variables were tested, including measures of the extended network, but only two were found to have an effect: whether the individual was married or not; and whether he or she was living alone or not (13). Table 5 presents data on admissions to specialty mental health facilities for inpatient and outpatient care by living situation, and the increased risk for those living alone shows up strongly.

Table 5. Admission rates by family status: United States, 1970 (30).

Persons Over 14 Years Old Per 100,000 Population	Mental Hospitals		Outpatient Clinics	
	Male	Female	Male	Female
Living alone	840	317	1,530	931
Living with a family	222	178	396	537

At the present time, the best evidence that an individual's extended social network has an affect on risk for mental disorder relates to community integration. In Stirling County, Nova Scotia, disorganized communities had twice the impairment levels of integrated communities, even with age, sex, and social class controlled (24). In human communities, crowded areas tend to have high rates of treatment for mental disorders, but, when factors related to social class are controlled, the relationship usually diminishes sharply or disappears. There are some community studies of extremely dense housing situations in which no strong effect of crowding by itself has been observed (7).

RECOMMENDED RESEARCH

Programs of preventive intervention can be based on knowledge of risk factors, causal factors, or efficient causes. Sound evidence of an efficient cause is preferable. An example from public health is the connection of certain species of mosquitoes to the occurrence of malaria, where the draining of swamps is the intervention. In psychiatry, things are rarely this simple, but it is reasonable to use a preventive intervention in an experimental fashion to establish the relative efficiency of a known causal factor.

Such experimental epidemiology is very tricky, however, because most of the disorders we study have many parallel chains of causation, and no single chain is likely to be connected to a large percentage of cases. For example, starting with table 1, we know that certain ethnic statuses have higher rates of affective disorders, and, since ethnic status is relatively immutable, it is a potential cause. We might therefore design a preventive intervention around a modifiable biological factor that is associated with affective disorders and with the most susceptible ethnic groups. The problem is that the difference in rate of affective disorders between groups could be totally due to different levels of stress or material resources in the different ethnic groups or to any other of the causal factors given in table 2. We would have wasted our resources.

A program of preventive intervention is even more problematic for risk factors in the lower part of table 1, whose causal direction is unclear. If the relationship turns out to be due to selection, intervention is limited to secondary and tertiary prevention.

A final use of the risk ratios in table 1 is as an aid to casefinding for intensive longitudinal study of the natural history of the mental disorders. Here the goal is to reduce the cost in obtaining a sample of cases, and it does not matter whether the relationship is causal or not. As an example, most of the high-risk studies of schizophrenia focus on children with one schizophrenic parent. These children have 10 times the general risk for schizophrenia, and the savings in cost are on the order of magnitude of the relative risk. The problem is that one can generalize only to that special population from which the sample is drawn. In the example of high-risk studies of schizophrenics, the limits to generalizability are severe: Children of schizophrenics make up only 10 percent of the population of schizophrenics; cases are usually located through schizophrenic mothers, who are unusual because many schizophrenics do not have children; and so forth. Yet this particular high-risk strategy for case location is more defensible than one based on the mutable demographic factors because the genetic variable is, at least, known to be causal.

Generalizability is a problem for research based on risk factors as casefinding aids, but it is not a crucial flaw. Obviously, we would be happy to prevent or help 10 percent of the schizophrenics. The problem of generalizability only means that we have

to be more careful, and when we adopt this strategy with noncausal risk factors, they must be stronger than is the case for causal factors or efficient causes. A relative risk of 10 to 1 or more is needed, in my opinion. In table 1, the only relationships that approach this magnitude are the association of social class and employment status with schizophrenia.

The only demographic risk factor which does not limit the generalizability of results is age. If one has limited research resources with which to conduct a longitudinal study, clearly one should focus on the age of highest risk. Only for schizophrenia do we have reasonable age-specific incidence rates, and here the 20-year period from 15 to 35 years is the focus.

These considerations lead to the following general recommendations:

1. Experimental preventive interventions for demographic and ecologic variables are not warranted at this time.

2. For immutable demographic and ecologic variables, cross-sectional research to identify the efficient cause(s) is justified. If such efforts are successful, experimental manipulations of the specific cause may or may not be feasible.

3. For mutable demographic and ecologic variables, longitudinal research is necessary to establish the direction of causation. The specific nature of the cause has to be established prior to preventive interventions, as in number 2 (above).

4. Aside from age, demographic and ecologic variables should not be used as aids to casefinding because the increase in efficiency is offset by the loss in generalizability of results and by difficulty in designing interventions.

Since this meeting is oriented toward longitudinal research, I will give some examples of the type of longitudinal research that would establish the direction of causation for some important risk factors (number 3, above) that would be highly likely to yield identifiable causes and that could easily lead into manageable experimental interventions.

Table 4 summarizes an enormous body of research and can help in guiding future research. Other things being equal, we want to concentrate on causal factors which have many "Xs" in their rows and demographic variables which have few "Xs" in their columns. If a causal relationship between marital status and mental disorder were established, there is a relatively delimited body of theory, connected to stress and social supports, with which to explain it. The only other variable that comes close to this relative simplicity is employment status, which has only the added complexity of the material resources explanation.

From this perspective, the most promising research would be designed to establish the causal relationship of employment and marital status to risk for mental disorders. The first step is a brief-longitudinal study in which employment, marital, and mental status are established at two points in time in a sample large enough to yield a minimum of 30 or so persons who change from employed to unemployed, or from married to not married, during the interval. Available data sets on longitudinal occupational histories

indicate that a sample of 3,000 over a 1-year timespan may be enough. If so, then this first step may be accomplished soon through the Epidemiologic Catchment Area Program.

A second study that could be done is a 20-year longitudinal study of primary social networks and mental disorders. This study would capture a great deal of information about social networks, stress, marital status, and employment status because of the overlap of these variables. Observe that marital status and employment status are thought to be important risk factors for mental disorders because of their relationship to social networks (table 4). They tap the two major domains of social networks: the occupational domain and the household domain. Unemployed or nonmarried persons almost automatically have smaller networks. Also, observe that they link up to primary social networks, which are probably more important as risk factors than extended networks. Finally, consider that stress and social networks are not conceptually very distinct, especially in a longitudinal approach. Life-event stresses, for the most part, are sudden changes in primary social networks. Some investigators have argued that social supports act to buffer the impact of sudden stresses, and, statistically, this buffering has been studied as an interaction effect between measures of stress and measures of social support. But this is an inadequate characterization of the process. In this proposed study a year-by-year monitoring of the social network of the individual would start at age 15, before the age of risk for at least some of these disorders. The age of 15 is good also because employment and marital status are identical for the entire population, and there is relative homogeneity in the availability of social networks. Age 15 is the latest age at which a cohort of individuals can be identified that is not too biased by death, emigration or institutionalization—that is, most 15-year-olds are in the school system. Finally, the school system provides for relatively easy administration of tests or interviews to large populations, once initial access to the school system is obtained.

This research ought to establish the causal effect of social networks, and of the change in social networks we call life-event stresses, on mental disorder. It also ought to show how employment and marital status and changes in these statuses are intertwined in the causal nexus. Finally, it would give a lot of basic research data on the life history of the normal individual and his social network. If this research shows that social networks, marital status, and employment status are relatively efficient causes, then programs of intervention are possible. Employment status is manipulable by an income-maintenance experiment. Manipulating marital status is not possible, but it is possible to manipulate the primary social network by offering new living situations to isolated persons which, through structural arrangements like proximity and sharing of communal facilities, place them in a dense social network.

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DISCUSSION

Dr. Marks: I wonder about the applicability of this. Let us say we do find in precise terms that employment, community integration, and variables like that are relevant. What can a body like NIMH realistically do? Changing variables like that is in the political sphere.

Dr. Regier: That is certainly a relevant issue. You are quite right; we are not in the social engineering business at NIMH. But if we are unable to manipulate these demographic factors, identifying them will nevertheless lead to the kinds of studies Dr. Kety discussed: What factors constitute the characteristics of lower social class? What happens when a marriage breaks up or when there is no marriage, in terms of social supports?

We can also consider these demographic and sociological variables as concentrating mechanisms which can focus on their components for a more intensive study, even if gross manipulation of social and political structures is not possible.

Dr. Kramer: One aspect of Dr. Eaton's material needs to be noted. Most of the studies he quoted are based on rates of first admission to mental institutions. This index—the first admission rate—measures another kind of risk, namely, the risk of a person with a specified mental disorder being admitted to a mental institution for the first time. Such a risk differs from the risk of a person developing the disorder.

The following equations illustrate this point:

If in population group, i,

N_i = number of persons in the mid-year population of the year in question (an approximation to the desired quantity),

a_i = number of persons becoming mentally ill during the year (first attacks),

h_i = number of persons first hospitalized during the year among the a_i,

h'_i = number of persons first hospitalized during the year among those who had become mentally ill in previous years and who had never been hospitalized,

then

$$I_i = \text{incidence rate for the year} = \frac{a_i}{N_i} ,$$

and

$$F_i = \text{first admission rate for the year}$$

$$= \frac{h_i + h'_i}{N_i} = \frac{a_i}{N_i} \cdot \frac{h_i + h'_i}{a_i}$$

that is,

$$F_i = I_i \cdot \frac{h_i + h'_i}{a_i} \cdot$$

Thus, the annual first-admission rate is a function not only of the incidence rate of mental disorder but also of the ratio of cases first hospitalized during the year, regardless of year of onset, to annual new cases. Indeed, the ratio of first admission rates in two population groups is equal to the ratio of the incidence rates only if:

$$\frac{h_1 + h'_1}{a_1} = \frac{h_2 + h'_2}{a_2} \quad ;$$

that is, only when the ratios of the total number of persons first hospitalized during the year to the number becoming mentally ill during the year are equal in the two groups.

Let us now apply the above to the use of first admission rates for schizophrenia as the basis for determining the relative risk of the divorced developing that disorder as compared to the married. It is quite clear that the only time the relative risk for schizophrenia as determined from annual first admission rates for that disorder equals the relative risk as determined from annual incidence rates is when the ratio of the total number of divorced persons with that disorder who are first hospitalized during a year to the newly occurring cases among the divorced is equal to the corresponding ratio for the married.

Another fact of importance is that diagnostic bias can lead to spurious measures of risk. To illustrate, the reported first admission rates into a mental institution for schizophrenia have always been much higher for blacks than for whites. A study by R.J. Simon et al. (Depression and schizophrenia in hospitalized black and white mental patients. Arch Gen Psy 28:509-512, 1973) illustrates the extent to which the diagnosis a patient receives (for example, schizophrenia) depends upon the hospital psychiatrist's diagnostic habits.

I also want to comment on the use of prevalence data for the identification of risk factors associated with a mental disorder. The point prevalence rate of a disorder as of a given date in an actual population is a complex index. The numerator of the rate for persons in a given age group, say 35-44 years, is a function of the incidence rates that occurred at earlier ages as well as in the specified age group and two variables that affect the duration of the disease between dates of onset and the survey date, namely

the "cure" rate and the fatality rate for persons with the disorder. Thus, two types of risk factors are associated with prevalence: those that affect incidence and those that affect duration.

In a stationary population with stable incidence rates and durations for a disorder, the relationship between prevalence and incidence is quite simple: Prevalence equals incidence x duration; i.e., prevalence equals the product of the annual number of new cases and their average duration. Consider the ratio of the prevalence rate of schizophrenia for the divorced to that for the married in such a population:

$$\frac{P_d}{P_m} = \frac{I_d \times (\text{Average duration of divorced cases})}{I_m \times (\text{Average duration of married cases})}$$

This equation highlights several important points. First, the only time the ratio of prevalence rates is the same as that of the incidence rates is when the average duration of the condition in each group is the same. Second, the ratio of the prevalence rates for a given disorder for two different population groups can be higher or lower than the ratio of the incidence rates depending on the value of the average durations. To illustrate, the prevalence rate of tuberculosis was found to be **lower** in blacks than in whites, while the incidence rate was **higher** in blacks than in whites. These differences were explained by the fact that the case fatality rate (i.e., the frequency with which persons with tuberculosis die of the disease) for blacks was considerably higher than the corresponding rate for whites. That is, duration of the disease was considerably less in blacks than in whites.

Prevalence surveys of a population, such as the ECA surveys, are an important source of cases for investigations of risk factors associated with a given disorder. When designing case-control studies to determine risk factors associated with a disorder like schizophrenia, investigators should be aware of the fact that the schizophrenics detected in a prevalence survey are a heterogeneous group. The group contains "new" cases, i.e., cases with relatively recent onsets, as well as chronic cases. Since the chronic cases are the survivors of earlier cohorts of "new" cases they differ from the "new" cases found in the survey not only in demographic and socioeconomic characteristics but in a variety of other characteristics as a result of various treatment experiences, hospitalization episodes, lifestyles, and other factors that may influence the course of the disease and survivorship from date of onset to the survey date. It is important for investigators who are designing risk factor studies to be aware of these differences in their selection of cases and controls, in their data-analysis plans, and in their interpretation of whatever differences may be detected between cases and controls.

Dr. Bruce Dohrenwend: I have two questions. One concerns the relative risk according to class for major and minor affective disorder. I would have read the evidence as indicating a strong inverse relationship for current prevalence, which holds for both minor and major.

Dr. Eaton: I think the data on major depressive disorder come from Weissman and Myer's review, and the difficulty is that there is a difference between lifetime and current prevalence. The relationship does not apply to lifetime prevalence.

Dr. Bruce Dohrenwend: The other question concerns the "X" marks under demographic variables opposite causal factors. Would you tell us how you excluded culture as related to marital status, or social integration in relation to employment?

Dr. Eaton: Well, it is a judgement. Usually, the "X" means there are data to indicate a relationship, like data that indicate differences in current natal mortality by social class, and it usually means there is a clear, plausible theory to explain the risk factor. Culture and socialization I thought of as long-term processes, not easily changeable in the course of a marriage.

I resisted the impulse to put an "X" mark in every box in trying to show some direction.

Dr. Kety: One of the problems in recommending a strategy for research in the present climate is that it might be adopted without thoughtful and critical review. There is a big difference between risk factors and etiological factors. I do not think we ought to emphasize risk factors and their modifiability at the expense of etiological factors as the basis for a national strategy. You are not going to prevent women from being female, a fact which excludes sex as a modifiable risk factor, but if there is a big difference in the risk for depression between females and males, that is a very important clue to the etiology of depression which should be followed up.

Dr. Regier: One of the things that we could usefully learn from a risk-factor type of study is whether some of these differences between men and women do indeed hold up in large general population studies as well as in clinical studies. Will we find the same sociodemographic differences between persons with and without mental disorders in a total population that we find in a preselected population that comes into a clinical setting? Possession of that type of information may make the biologists' efforts much more useful. Validation of risk factors is thus **one part** of a national strategy aimed at understanding the etiological factors hidden within them.

Dr. Klein: I want to talk specifically about the relationship between marriage and schizophrenia because there are two important relationships. One is that schizophrenics are far less often married, and the second is that, prognostically, married schizophrenics do much better than unmarried schizophrenics.

We looked at the childhood and adolescent development of schizophrenics, and we were able to show that those who have been friendless and hard to get along with did not get married and did poorly. This again illustrates that risk factors are associates and cannot be simply viewed in a causal way. In terms of research strategy, I would be concerned about the short-term antecedents rather than a 20-year followup.

Dr. Marks: I would like to respond to Seymour's point that risk does not equal etiology. Think of the prevention of cholera by Snow. When he took the handle off the Broad Street pump, he did not know that cholera existed, but it was a very good preventive strategy. And though we often do not know quite how poverty leads to various pathologies, if we had a strategy for reducing poverty, we could probably reduce a great deal of pathology.

Dr. Fleiss: A more immediate example of not waiting to know etiology to implicate a factor is that we are not smoking here. I do not think any of us knows how cigarette smoking affects all the organs it does, but we are controlling for what is known to be a risk factor for so many disorders. Furthermore, we have known sex differences

to exist in many disorders for centuries; but who is doing research into why males differ from females in these respects? We have not in all these decades and centuries, and I wonder why. Maybe there is a feeling that it just will not pay off.

Dr. Guze: Well, in some studies they are doing it. I do not know about psychiatry, but it is true for general medicine.

Dr. Kety: When there is nothing else to go on, then perhaps it is useful to go after prevention of risk. Certainly no one would object to doing away with poverty, but the slow progress there, which cannot be attributed to lack of scientific knowledge, should not deter us from pursuing the less obvious etiological research through which pellagra and paresis have been practically eradicated. I would regard the evidence that water from a particular source led to cholera or that cigarette smoking is a crucial etiological factor in lung cancer as more compelling and better justifying specific preventive intervention than any of the evidence we have today for specific environmental factors in the etiology of the mental illnesses.

Dr. Guze: But it is not either-or. Those become political-social judgments. The scientific community really ought not to be forced into that kind of choice. You have to put some eggs in the basket of fundamental research and some eggs in the basket of other studies.

Dr. Garmezy: We have a good example of the type of debate that ensues when a risk variable is accorded etiological status. When Mednick and Schulsinger first presented their evidence that a history of pregnancy and birth complications (PBC) was present in their high-risk sample to a significantly greater extent than among the controls, they discussed it in the context of a diathesis-stress model of schizophrenia. In that formulation the PBCs served the role of potential stressors. Two discussants of the paper, Leonard Heston and Barbara Fish, took the view that these were more likely to be manifestations of the schizophrenic genotype. There they were, with two reasonable but unresolved propositions.

LIFE STRESS AND PSYCHOPATHOLOGY

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INTRODUCTION

This paper gives little time to what might seem to be a fundamental question: Is life stress related to psychopathology? When one considers the full range of evidence from war and other extreme situations (14, pp. 116-124) to stressful life events occurring in ordinary community settings (15), the answer to this question seems to be affirmative though not very informative. It is, at best, the starting point from which to turn to the more interesting question: **How** is life stress related to psychopathology?

It is this second question on which we focus. In asking it we make two assumptions. First, we assume that there is some kind of relationship between life stress and psychopathology, an assumption that, as is apparent when we discuss alternative hypotheses about the nature of the relationship, is not necessarily a radical one. Our second assumption is that life stress is a complex process that can be conceptualized in terms of three major components: life events, personal dispositions, and ongoing social situations.

WHAT IS A STRESSFUL LIFE EVENT?

The stressful life events with which we are concerned at this point are those that are proximate to, rather than remote from, the onset of a disorder. For example, this category includes the recent death of a friend or relative but not the fact that an adult's father died when he or she was a child. The latter event is not irrelevant to life stress but is subsumed under personal dispositions, since we assume that the early death of a parent can affect an adult's behavior only insofar as its impact was internalized.

Although some studies have been directed at the question of what qualities of life events are related to psychological problems, most have examined psychological symptom scores, whose diagnostic implications are unclear, rather than cases of

diagnosed psychopathology. Furthermore, many studies of life events and diagnosed psychopathology are case studies without controls. We have found only five studies that provide information about the kinds of events that are specific to cases of diagnosed psychopathology in contrast to nonpatient controls. Our review concerning the qualities of life events that are related to psychopathology focuses on these case-control studies of relations between diagnosed schizophrenia, clinical depression, or neurosis and life events. The findings, not surprisingly, depend to some extent on the kind of psychopathology being studied.

Two case-control studies have shown that the number of life events reported by schizophrenics before onset of an episode was significantly greater than the number reported by controls for a comparable period. One study, by Jacobs and Myers (23) in New Haven, focused on a survey of 62 first admissions; the other, by Brown and Birley (5) in London, was concerned with 50 patients admitted for acute episodes of schizophrenia. Although the consistent finding of these two studies was that there was a significantly higher rate of life events in their reporting periods, 1 year in the former and 3 months in the latter study, for patients compared to community controls, this excess was due mainly to events that could be dependent on the patients' mental condition. It is of considerable interest, therefore, that Brown and Birley, who dated the occurrence of events within 1-week periods, found that events that were independent of a person's psychiatric condition occurred more frequently in the 3-week period preceding episodes of schizopherenia than in a comparable period in the lives of their controls. Forty six percent of the patients but only 12 percent of the controls experienced at least one independent event in this 3-week period. This difference was not found in earlier 3-week periods. Moreover, this finding is not an isolated one, since Leff and his colleagues (28) found a relatively high frequency of events in the period just prior to relapse in a sample of schizophrenics being treated with phenothiazines in the community. In addition, Brown and Birley showed that their result held regardless of first admission versus readmission status of the patient, and also for patients experiencing first episodes versus those experiencing relapses.

In these studies the events included were both desirable and undesirable, suggesting that any kind of change may increase a person's risk of experiencing a schizophrenic episode. It should be noted, however, that Brown and Birley conceived their events to be stressful not because they entailed change but because they "would for most people be likely to be followed by a strong negative or positive emotion" (5, p. 66).

In his case-control studies of life events and clinical depression, Paykel (31) found that undesirable events, but not desirable events, were reported in excess in the 6 months prior to the onset of depression. He also identified a class of events that he labeled "exits," in which a person leaves the social field of the subject. The events which Paykel included in this category were death of close family member, marital separation, divorce, family member leaving home, child getting married, and son being drafted. Paykel found that the presence of one or more of these events was strongly associated with onsets of depression. While only 5 percent of controls reported one or more exits in the 6-month reporting period, 25 percent of the depressed patients reported at least one such event.

Brown and Harris (6) also reported a difference in recent life events between depressed women, whether treated or untreated, and nondepressed community controls. They found that depressed women had experienced an excess of a class of events that

Brown and Harris labeled "severe," in the period, on the average, of 38 weeks before the onset of depression. Specifically, 61 percent of treated cases and 68 percent of untreated cases, but only 20 percent of community controls, had experienced at least one such event.

Unfortunately, Brown's and Harris' concept of severity embodies two components of the life-stress process, the occurrence of an event together with those aspects of the ongoing social context that are judged by raters to endow the event with a moderate or marked degree of threat that is likely to last more than 1 week. While these judgments were tested and found to be reliable across raters (36), the criteria on which they are based are often specific to particular events and do not lend themselves to generalized description. These results cannot, therefore, be compared directly with Paykel's.

In an exploratory study of the difference in recent life events experienced by 34 diagnosed acute neurotic cases found in general practices and in matched general practice patients free of psychiatric disturbance, Cooper and Sylph (10) adopted Brown's and Harris' procedure for identifying severe events by means of ratings of long-term contextual threat. They found that 47 percent of their neurotic patients but only 6 percent of their controls had experienced at least one severe event during the 3-month comparison period. However, adopting another classification employed by Brown in his study of schizophrenics, but not in his study of depressed women, they did not find a significant difference in the number of events experienced by cases and controls that were independent of the illness. This statistical result may, however, be a function of the small number of subjects in the study, since 53 percent of the cases and only 26 percent of controls reported at least one independent event.

What have we learned about the nature of stressful life events from studies of diagnosed cases of psychopathology? Studies to date suggest that any life event that involves change may be stressful for persons otherwise at risk of schizophrenia, but only certain types of life events may be stressful for persons otherwise at risk of clinical depression or neurosis. These findings imply that stressfulness is not a simple, unidimensional property of life events and that more research is needed to map associations between event properties and various kinds of psychopathology.

In carrying out such studies, we must not lose sight of a crucial distinction that has been attended to only erratically in research to date—the distinction among life events in terms of their functional relation to psychopathology. For example, in his research on schizophrenia, Brown analyzed separately events classified as independent and events classified as possibly independent of the subject's psychopathology (5), as did Jacobs and Myers (23). Cooper and Sylph (10) made the same distinction in their study of neurotics. However, neither Brown and Harris (6) nor Paykel (31) made this distinction in their studies of clinical depression. Given the problem of insidious onset of many types of psychopathology, clear inferences concerning causal relations between life events and episodes of psychopathology cannot be made unless events that are inherently independent of pathology and events that may be part of a pathological process are separated in analyses of their relations to pathology (cf. 12).

WHAT PERSONAL DISPOSITIONS ARE RELATED TO THE LIFE-STRESS PROCESS?

Hypotheses concerning the nature of personal dispositions involved in relationships between life stress and psychopathology are of four general types. These types are not necessarily mutually exclusive. One focuses on genetic risk factors as a predisposing condition for particular types of psychopathology. We do not elaborate on this hypothesis since it will be discussed by others more competent to do so.

Another hypothesis is that prior psychopathology predisposes the individual to subsequent episodes of psychopathology. While the reality of this kind of risk factor is not in doubt, the mechanisms that lead to new episodes are not well understood. We propose studies directed at testing alternative models of the life-stress process that are related to this issue.

Let us turn to the third type of hypothesis. We said at the outset that we would be concerned first with stressful life events that are proximate to, rather than remote from, the onset of a disorder. We noted, however, that we are not assuming that remote events are irrelevant, but only that it is more convenient to consider such events as they might influence personal dispositions later in life. Is there evidence, then, that stressful events early in life do, in fact, render the individual more or less vulnerable to stressful events later in life?

There are quite consistent findings that homes broken by divorce or separation in childhood are associated with late antisocial behavior (cf. 33). The results of research on the later effects of death of one or both parents during childhood appear to be much less consistent (20). It seems possible, however, that the apparent inconsistency has been due to insufficient attention to whether bereavement took place early or late in childhood. There are now at least three studies with results suggesting that death of one or both parents before age 11 is associated with vulnerability to depression (6) and/or severe psychological distress (13; 25, pp. 167-169) among adults in samples from the general population who experience stressful life events. There is considerably less information on whether early experience with some types of events tends to decrease vulnerability to later stressful events. It is intriguing to consider whether there may be such inoculation effects (cf. 4).

The fourth type of hypothesis considers ways in which normal variations in personality may affect an individual's response to stressful life events. Much has been learned in the last two decades from clinical observations, observations in natural settings, and experimental studies about effective psychological defense and coping responses to stressful events (e.g., 21,22,26). At the same time, hypotheses have been developed concerning the nature of individual differences in disposition that account for pathological outcomes related to stressful life events.

As one example, an hypothesis concerning individual differences in vulnerability to stress-related psychopathology grows out of Rotter's social learning theory and his concept that individuals have a generalized expectancy about the extent to which they control the rewards, punishments, and, in general, the events that occur in their lives. Rotter (32) conceived this expectancy, which he labeled "locus of control," as varying on a dimension from internal to external. Persons at the extreme internal end of the locus-of-control dimension expect to be in control of their life events to a high degree. In contrast, persons at the extreme external end of the locus-of-control dimension expect that their life events will generally be controlled by others or by fate. Although there is some controversy concerning the relation of locus-of-control expectancy to vulnerability

to pathology, the hypothesis with the most extensive empirical support is that persons with an external locus-of-control expectancy have greater proneness to psychopathology than those with an internal locus-of-control expectancy (e.g., 27, Ch. 7). In fact, in some studies, internal locus-of-control expectancy has been equated with competence, coping ability, and relative invulnerability to debilitating effects of stressful events (7, pp. 59-60).

In general, we are suggesting that, where theory or empirical findings suggest meaningful hypotheses, normal variations in personality should be studied as part of the life-stress process. We have provided one example of this kind of personality variable.

WHAT SOCIAL CONDITIONS ARE RELATED TO THE LIFE-STRESS PROCESS?

Complementing efforts to find factors within the individual that affect his risk of psychopathology related to stressful life events are more recent attempts to identify social factors in the individual's environment that affect this risk. One of the most influential hypotheses in the recent literature on life stress states that social support mitigates the effects of stressful events (8). Secondary analyses of data not specifically designed to test this hypothesis have suggested that highly stressful events combined with low social support are significantly more pathogenic than highly stressful events combined with high social support or less stressful events with high or low social support (19).

What is the structure of the support systems available to an individual? Although early efforts to conceptualize social supports tended to focus on formal helping agencies, such as mental health centers (8), work has also been done on analysis of the structure of varied forms of informal support systems, particularly family, neighborhood, and friendship networks (16). What is needed now in measures to be used in stress research is objective information about social networks and their structures, unconfounded with the quality of an individual's participation in these networks. Without this separation the relative contribution to the life-stress process of an individual's personality as against his or her social situation cannot be assessed.

Another question is: What functions can be performed by the various structures in an individual's support systems? Although to date most studies of social support have, by implication, emphasized emotional support, some exploratory studies suggest that it is equally important to investigate the availability of instrumental support during life events (9). Financial support is probably an important type of instrumental support in many life events. For example, if there is illness in the family, is there adequate insurance available, or, if not, is there someone in the person's informal network who will help out or a community agency to serve this purpose? Other types of instrumental support may be specific to particular life events. For example, in the case of serious illness, can the person obtain adequate medical care? Does the new mother have someone to turn to for advice about the care of her baby? Exploratory studies suggest that different functions may be served by different support structures (30). For example, friends and acquaintances may be able to do more than family about helping a person find a new job, but family may be a better source of help with problems in personal relationships. Thus, at least in our present state of ignorance about how support systems function in the life-stress process, it is important to obtain as complete a description as possible of potentially supportive structures.

HYPOTHESES ABOUT THE LIFE-STRESS PROCESS

The majority of studies of life stress and illness have been concerned primarily or exclusively with one or another of the three types of constructs that we have discussed: stressful life events, personal dispositions, or social conditions. Up to this point we have dealt with these constructs singly. The task now is to integrate them into hypotheses about the life-stress process, a task that has received increasing attention recently. In theoretical and empirical studies investigators have developed at least five different hypotheses, as schematized in figure 1.

The first hypothesis, in figure 1A, indicates that cumulations of stressful life events cause adverse health changes. This model was developed empirically in studies of extreme situations such as combat and concentration camps. It has been generalized to normal civil life in terms of a pathogenic triad of concomitant events and conditions that involve physical exhaustion, resulting often from severe physical illness or injury; loss of social support, as a result, for example, of geographical relocation; and the fateful negative events other than physical illness or injury over whose occurrence the individual has no control, such as death of a loved one (11). It is also the model that underlies the early work of Holmes and Rahe and their co-workers. This could be called the **victimization** hypothesis.

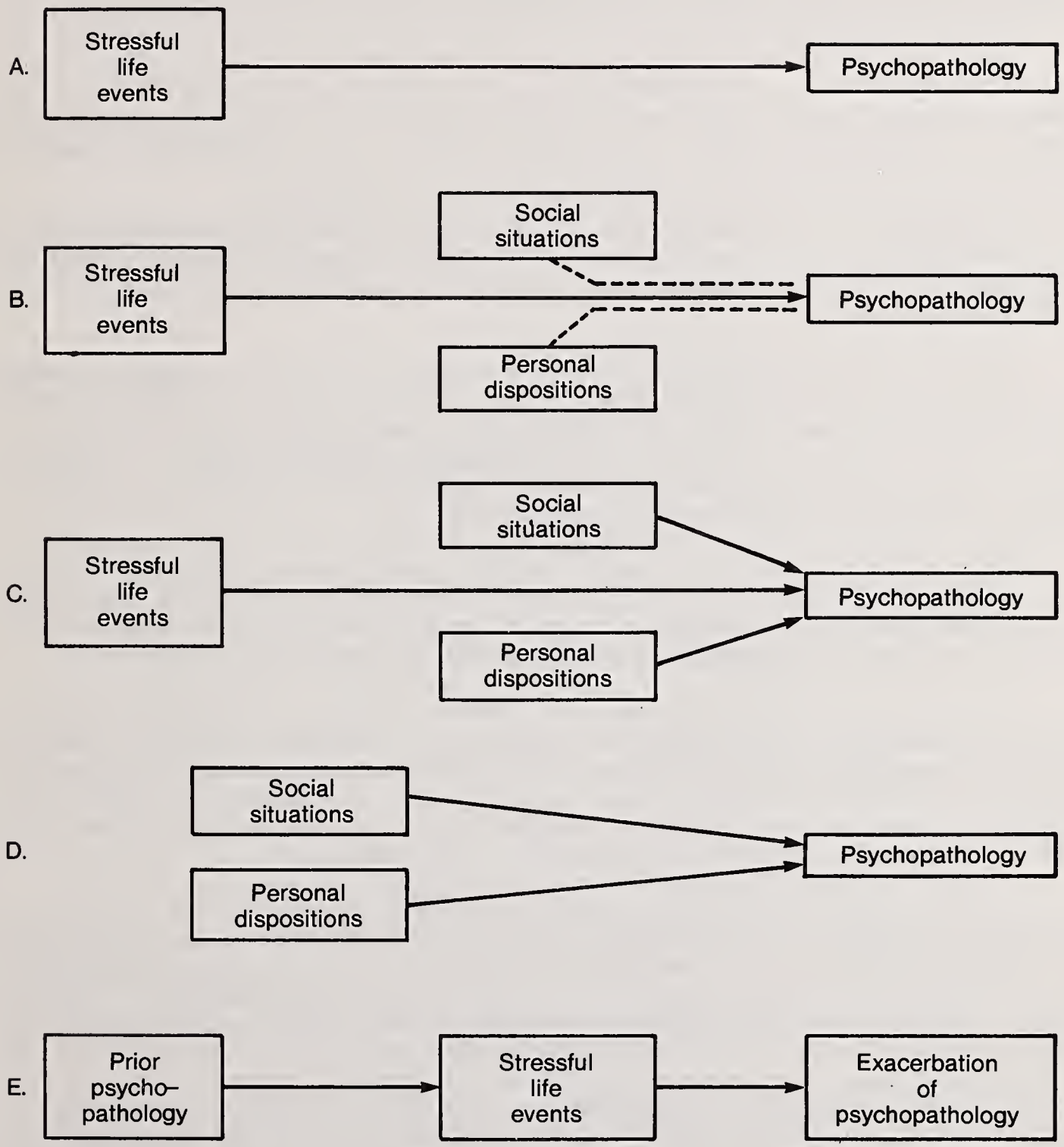
The second hypothesis, in figure 1B, supposes that pre-existing personal dispositions and social conditions moderate the causal relation between stressful life events and psychopathology. This hypothesis underlies the literature on vulnerability involving conceptions such as coping ability and social support. It was also proposed by Zubin and Spring in their discussion of the etiology of schizophrenia (37) and by Brown and Harris (6) in their social model of the etiology of depression. This could be called the **vulnerability** hypothesis.

The third hypothesis, in figure 1C, contrasts with the second in that, rather than moderating the impact of stressful life events, personal dispositions and social conditions make an independent causal contribution to the occurrence of psychopathology. This hypothesis received empirical support in a study of psychosocial symptoms by Andrews and his colleagues (2) and was also proposed by Tennant and Bebbington (35) as a better fit than the second hypothesis to the data presented by Brown and Harris (6) in their study of social factors in the etiology of depression. This could be characterized as the **additive burden** hypothesis.

The fourth hypothesis, in figure 1D, is another and further modification of the second. It denies any role to life events, proposing instead that stable personal dispositions and social conditions alone cause the adverse health changes. This hypothesis was presented by Gersten and her colleagues as an explanation of changes in children's psychological symptom patterns (18). The method they use in developing the empirical basis for this hypothesis is, however, open to criticism (29). This hypothesis, in contrast to the previous one, could be called the **chronic burden** hypothesis.

The final hypothesis, in figure 1E, raises the crucial issue of the direction of the causal relation between life events and psychopathology. It proposes that the presence of a disorder leads to stressful life events which, in turn, exacerbate the disorder. In empirical tests this hypothesis was supported by a study of chronic patients (17) but not by a study of neurotics (34). This might be called the **proneness** hypothesis, in the sense that proneness to stressful events is the central mechanism posited.

Figure 1. Five hypotheses about the life stress process.



These hypotheses are neither exhaustive nor mutually exclusive. They provide, nevertheless, a framework for designing research to advance our understanding of relations between life stress and psychopathology.

RESEARCH DESIGN FOR STUDY OF LIFE STRESS AND PSYCHOPATHOLOGY

We suggest that tests of alternative hypotheses about the relation of life stress to psychopathology be done in a longitudinal case-control design with groups that vary with respect to genetic and/or early experiential risk factors. Cases should include two subgroups: those with and those without genetic and/or early experiential risk factors. Controls with no history of disorder should include the same subgroups.

In addition, the inclusion of cases of different types of psychopathology within a single case-control study is essential for differentiating factors related to distress and other adverse outcomes in general from those that are specific to particular types of psychopathogy (cf. 3,24).

Baseline measures should include not only standardized research diagnostic procedure with all controls as well as cases, but also measures indicating nonpathological personal dispositions, particularly personality traits and certain early life experiences, in cases as well as controls. Current social situations, including social and material supports and demands, should also be carefully measured for all subjects. Finally, a baseline measure of recent life events should be taken.

The baseline measures of life events must be dated in relation to the onset of the episode. Although it is far easier to date onset of treatment than onset of an episode (cf. 1), use of the former as the reference point for baseline life-event measures leaves the nature of the relationship between life events and the onset of disorder ambiguous.

In the prospective part of the study, both short-term and long-term followup measures are needed. The occurrence of life events in relation to the occurrence of episodes or exacerbations of the disorders under study should be monitored, with careful dating, on a relatively short-term basis, say every 2, 3, or 4 months. A longer term followup of a year or more should, minimally, repeat the diagnostic procedures and might well repeat other baseline measures to test their stability.

In this research, it will be of utmost importance to pay careful attention to measurement problems that have made results from much previous research on life stress and psychopathology difficult to interpret. It is all too easy to confound measures of life events, personal dispositions, enduring social conditions, and psychopathology with one another. This kind of confounding guarantees results that, at best, are uninterpretable and, at worst, can lead to erroneous conclusions. Enough progress has been made in the clarification of these measurement problems so that there is no need to repeat past mistakes, for example, failure to distinguish between life events that are independent of a subject's mental condition and those that are not, or between the structure of objective social networks and their effectiveness, or between these networks and personal dispositions related to having friends or not having them.

In conclusion, there is now enough correlational evidence so that the interesting question is not whether life stress is associated with various types of psychopathology but what hypotheses best account for these relationships. Some of the hypotheses that

we presented earlier specifically discount the role of recent stressful life events as etiological agents; some have a place for personality variables and genetic vulnerability as etiological factors. Taken together, they hardly represent rampant environmental imperialism. Moreover, research design to test hypotheses of this kind provides a safeguard against continuing to do studies that merely document a position. It will provide, instead, tests of alternative hypotheses about the interplay of life stress, other risk factors, and various types of psychopathology. The testing of such hypotheses, we submit, is the next task of research on life stress and psychopathology.

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DISCUSSION

Dr. Guze: We have heard today that the children of schizophrenics begin to show psychopathology very early in the course of their development. We are also told that life stresses are reported at increased frequency during some interval before a psychotic break. Now, there seems to be a contradiction here. If you are going to study life stress in schizophrenia, how do you decide when the illness began?

Dr. Barbara Dohrenwend: I assume that, even when a subtle clinical examination can detect something in these high-risk children, they do not necessarily go on to have a full-blown psychotic break. Our hypothesis is that something is going on in the world they are living in also contributes to a more or less favorable outcome for these high-risk children.

Dr. Garmezy: The problem is not as difficult as Dr. Guze has stated it. First, I would not assert that most children or even many children of schizophrenic parents show schizophrenia at an early age. There is such a subset in the studies of Barbara Fish. Her reports have focused on deficiencies in neurointegrative functioning almost from the moment of birth of these high-risk infants. But that group is a very small subset of infants when arrayed against the large numbers of children of schizophrenic mothers who have been studied since that early research. In the Mednick-Schulsinger studies some children who initially were viewed as moving along a path of maladaptation, subsequently improved markedly in their adjustment. We would be wrong to suggest that the earlier observations were precursor indicators.

Finally, I would commend the positive description that Dr. Manfred Bleuler has provided for us in his discussion of the adaptation of children of schizophrenic parents in his volume, The Schizophrenic Disorders: Long-Term Patient and Family Studies (Yale University Press 1978).

Dr. Weissman: I think the question is: What is cause and what is consequence? If you cannot date the onset of the disorder, then it is difficult to say that the life event is not a consequence of an insidious disorder which has already begun.

Dr. Guze: That is true, but there is another possibility. By analogy with diabetes, it is one thing to say that life stress precipitates an episode of diabetic acidosis, and another to say it is related to development of the diabetic diathesis. The same kind of life situation can have a different effect at a different place in the evolution of the disorder. There are questions that most people in this field have not gotten to.

Dr. Regier: It is clear that the better we can define the dependent variable, be it schizophrenia or diabetes, the more precisely we can differentiate between the role of a life event at an early stage and, say, at a middle stage of the disorder.

Dr. Bunney: I think it is an important question—when did the illness start? It may be more difficult in schizophrenia than in depression. We spent a year studying about 40 depressed patients, and in most cases we had a pretty good gut feeling about when the illness started. It developed slowly, but you could find a point when the first symptoms started, then go back a few weeks to look at the stresses. What we found was a group of stresses before the first symptoms, and then stresses kept coming and may have had something to do with the escalation or the severity of the illness, either as cause or as effect.

Dr. Gershon: Dr. Dohrenwend said that not all the children who are at risk become ill, and therefore environmental factors such as life events must interact with the predisposition. But this disregards two important considerations. First, under any genetic hypothesis, not all the children of the schizophrenic mothers are at risk, so the reason that some are not ill may not be an environmental factor at all. Second, the environmental factor may have acted long before the start of your observations, like the cytomegalovirus that Dr. Kety spoke of.

Dr. Prien: Do any of these risk factors, alone or together, account for more than 10 or 15 percent of the variance in the criterion disorder? Are we any better off with the biological or physiological variables?

Dr. Barbara Dohrenwend: Very few studies have investigated several social and psychological risk factors simultaneously. The one that comes closest is by Brown and Harris. Their results suggest that the risk factors they studied account for a substantial portion (considerably more than 10 percent) of the variance at least in some groups, such as working class women.

I take these correlational findings to be of interest, even if they do not account for a large part of the variance, because it seems to me they should be followed up with respect to etiology. We have an obligation to try to find out what is going on here that is hinted at by the correlations.

Dr. Kramer: I am trying to visualize an ideal experimental design to measure the rate at which people who have experienced a given life event develop a disorder, as compared with the rate for those who have not experienced such an event.

Dr. Barbara Dohrenwend: I think the problem is a little different from that. You would have groups who differ in terms of genetic or other early risk factors. And you would predict that responses to similar events would vary between those groups.

Dr. Kramer: Well, it is essentially the same problem. If you are doing a prospective study of schizophrenia, you have to eliminate at the start those who are known to have had schizophrenia. Then you would have to compute incidence rates per person-year of exposure in each of these groups.

Dr. Coursey: This life-stress issue brings up a risk factor that has not been directly addressed. That is the cognitive mediation of some of these things: a person's style of thinking, how a person interprets his life events. This would seem to me to be a really important area.

Dr. Barbara Dohrenwend: We have suggested that, where there are hypotheses and evidence, cognitive processes should be considered. Locus of control is an example, because that is indeed a cognitive matter.

GENETIC VULNERABILITY IN PSYCHIATRIC EPIDEMIOLOGY

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INTRODUCTION

Within populations, the major identifiable predictor of vulnerability to severe affective disorders, chronic schizophrenia, panic disorder, alcoholism, and antisocial personality/criminal convictions is family history of the same disorder (table 1). Except for panic disorder, where adoption studies have not yet been done, all are transmitted despite adoption away from the biological parents in infancy, strongly suggesting genetic rather than cultural familial transmission. So far, psychiatric epidemiology has responded to these findings with clinical family diagnostic studies and by developing mathematical analytic models to analyze pedigree data. The major thrust of this paper is that the purview of psychiatric epidemiology should include, as elsewhere in medicine, the biological underpinnings, especially the biochemistry, that must exist for genetically transmitted diseases.[1] Identification of biological predictors of risk, including use of pharmacogenetic strategies to unmask vulnerability, is a major goal to be pursued. At this time, however, this is a research goal not yet achieved. The second thrust of this paper, then, is toward the application of current techniques of clinical diagnostic family studies to casefinding in populations, which currently appears to be the major preventive opportunity offered by current knowledge on genetic risk.

METHODOLOGICAL ISSUES IN PSYCHIATRIC POPULATION GENETIC STUDIES

Family Study

Clinical diagnostic study of pedigrees of patients, including adoption and twin studies, is the constantly required investigative method of psychiatric genetics. With the advent of standard diagnostic interviews and criteria for diagnosis, the reliability problem has been considered solved (30,56). Differences among investigators persist, however, in lifetime risk estimates in populations and in pedigrees of patients, despite

Table 1. Psychiatric disorders with family transmission data.

	Transmission Even After Adoption	Twin Concordance: MZ > DZ	Prevalence: 1° Relative > Population	References Or Review	Comments
Affective Illness	Yes	Yes	Yes	42	More severe forms heritable
Schizophrenia (chronic)	Yes	Yes	Yes	30	
Panic disorder/ agoraphobia	Not studied	Yes	Yes	4,9,46,47	
Alcoholism	Yes Males only	Yes	Yes	3,20,21,52, 53,55,62	
Antisocial personality/criminality	Yes 2/3 studies	Yes Most studies	Yes	3,6,8,23, 24,25,63	XXY and XYY karyotypes rare but associated with criminality

use of purportedly substantially identical methods and criteria. Recent estimates of population lifetime prevalence of panic disorder range between 1.7 percent and 8 percent (unpublished communications, M.M. Weissman, C.R. Cloninger). For major affective disorders, lifetime prevalence estimates range between 2.4 percent (17) and 21 percent (61). I believe these differences largely represent variation among projects in definitions of specific criteria and render absolute estimates of these prevalences not truly comparable between different groups of investigators. Nonetheless, the methods have become explicit enough to permit tentative conclusions about the different results.

When depression is defined as a more severe disorder, with hospitalization or incapacitation required before diagnosis is made, it is a relatively uncommon disorder, with 2 1/2 percent to 6 percent lifetime risk in the population, having a very strong familial concentration that fits genetic models for either single gene or multifactorial transmission (14). When defined according to the broader conception of the Research Diagnostic Criteria, the population lifetime prevalence is estimated at 21 percent (61), and genetic transmission was **excluded** in a recent careful analysis of family study data (50). The familial influence appeared to be a sibling-sibling cultural effect.

A summary of family-study estimates of lifetime risk in first-degree relatives of patients with affective disorders is offered in table 2, which is discussed elsewhere (42).

Table 2. Affective illness in first-degree relatives.

Bipolar Probands	Relatives At Risk	Morbid Risk (%) BP	UP
James and Chapman 1975	239	6.4	13.2
Gershon, et al. 1975b	341	3.8	6.8
Goetzl, et al. 1974	212	2.8	13.7
Helzer and Winokur 1974	151	4.6	10.6
Winokur and Clayton 1967	167	10.2	20.4
Perris 1966	627	10.2	0.5
Angst 1966	161	4.3	13.0
Smeraldi, et al. 1977	172	5.8	7.1
Trzebiatowska-Trzeciak 1977	289	11.4	0.0
Johnson & Leeman 1977	126	15.5	19.8
Petterson 1977	472	3.6	7.2
Mendlewicz and Rainer 1974	781	17.7	22.4
Unipolar Probands			
Angst 1966	811	0.3	5.1
Perris 1966	684	0.3	6.4
Gershon, et al. 1975b	96	2.1	11.5
Smeraldi, et al. 1977	185	0.6	8.0
Trzebiatowska-Trzeciak 1977	265	0.3	7.1

Table reprinted with modifications, by permission, from (42), where all references are given except Mendlewicz and Rainer (38).

In epidemiologic/diagnostic family studies, we may have had "overkill" in the number of family studies of clinical diagnosis in relatives of patients with major affective disorders, if we include studies from my group and the other large studies that are currently funded. Future studies, in my opinion, should have a specific biological or other etiological vulnerability hypothesis that they are testing, rather than be purely concerned with clinical diagnosis. There have also been more than enough "naturalistic" family history papers in the literature, where old case records are studied without followup of examinable individuals or where a single informant gives the entire family history which is then treated as if it were reliable data.

To my knowledge, no family studies of chronic schizophrenia, using the newer systematic diagnostic criteria, have yet been published.

Markers of Vulnerability

By themselves, empiric risk estimates based on disease prevalences in relatives do not contribute to identifying what the genetic risk factors are. But having identified which members of pedigrees are ill and which are well, the validity of an hypothesized vulnerability factor can be tested by its power to discriminate ill from well persons.

We can distinguish two types of vulnerability markers to a genetic disorder, the first associated with the pathophysiological process leading to illness, as distinguished from the second type, **linkage markers**, which identify on a chromosomal map single locus vulnerability factors without implications for pathophysiology (table 3).

The genetics of psychobiological characteristics in human populations and the development of linkage markers and identification of new polymorphisms are the scientific underpinnings of research into genetic vulnerability factors, as discussed elsewhere (12). One example is the recent advances in DNA technology that have produced a potentially vast number of identifiable polymorphisms of nucleic acid fragments produced by restriction endonucleases (64). These and similar advances, if pursued, can increase the number of available linkage markers in pedigree studies by several orders of magnitude and are expected by leading geneticists to give a complete map of the human genome by the year 2000. This would enhance the power of genetic analyses, allowing us to state with certainty whether single locus transmission was present in a given pedigree or well-defined disorder.

Population genetics of psychobiological characteristics is a recently opened area of research. Single locus codominant transmission of RBC catechol-O-methyl-transferase (COMT) and plasma dopamine-β-hydroxylase (DBH) was identified from studies of enzyme activity in hundreds of families (15,60). This led to identification of a biologically variant (heat labile) protein associated with the lower COMT activity (51). This was the first instance, to my knowledge, of population genetic methods based on quantitative activity measurements successfully predicting the existence of a variant protein. In the present context, it is worth noting that this is one of a class of studies that now falls in the cracks between epidemiology and psychobiology/ psychopharmacology funding areas, so that much of this work did not receive NIMH extramural program support.

Pharmacogenetic population studies are a potential source of markers of genetic vulnerability to psychiatric disorders. In a study of normal control twins, Nurnberger et al. (43) found that there is genetically controlled variability in behavioral excitement response to amphetamine, so that some persons did not have any excitement at all.

Plasma amphetamine levels were not correlated with this response, which appeared to be a function of noradrenergic reactivity. These findings have clear implications for identifying vulnerability to amphetamine abuse, even though this abuse is not considered a genetically transmitted disorder.

Table 3. Criteria for vulnerability markers.

Tests for a pathophysiological genetic marker
1. Presence of marker associated with illness in population
2. Within families of patients with the marker
a. relatives with marker tend to be ill
b. relatives without marker are protected in comparison
If all of above are true, the marker is necessary for the illness or contributes to vulnerability.
Tests for a linkage mapping marker
1. Single gene marker locus with two or more phenotypes (forms)
2. No form of marker associated with illness in population
3. Within families, one form of marker associated with illness, second form associated with nonillness
If all of above are true, illness vulnerability is transmitted at a single major gene locus near the marker on the chromosomal map (general exception: linkage disequilibrium).

Pharmacological challenge with agents that perturb specific neurotransmitter systems may expose differential sensitivity in patients versus controls and is a more straightforward application of psychogenetics to vulnerability markers. Recently Sitaram et al. (54) demonstrated increased sensitivity to cholinergic agonists in euthymic drug-free bipolar patients. Rapid eye movement (REM) sleep induction by arecoline, and pupillary response to pilocarpine, both distinguished bipolar patients from normal controls. Genetic studies of these findings are in progress.

CURRENT STUDIES OF BIOLOGICAL VULNERABILITY MARKERS

Platelet Monoamine Oxidase in Affective Illness, Schizophrenia, and Alcoholism

The leading biological hypotheses in virtually all the major psychiatric disorders for some years have centered around variation in neurotransmitters, so it is not surprising that many of the genetic studies in different disorders have involved enzymes related to neurotransmitters.

Platelet MAO was reported to be reduced in bipolar patients (41), in chronic schizophrenics (65) (but generally not in acute schizophrenics), and in alcoholism (57). These findings have been replicated by some but not all investigators in schizophrenia and affective illness, as reviewed elsewhere (15,18,22,49,66).

Platelet MAO activity is highly correlated between MZ twins and less highly correlated between DZ twins. Autosomal single gene inheritance of platelet MAO activity has been excluded by applying mathematical models to family data (15). Platelet MAO (type A) is distinct in at least one moiety of its amino acid sequences from fibroblast MAO (type B) (5), but it is not clear that the two types of enzyme are genetically independent. Fibroblast MAO has been tentatively assigned to the X chromosome by cell-fusion techniques (48). Platelet MAO activity is reduced in unaffected MZ co-twins of schizophrenics (65) and in first-degree relatives of bipolar patients (28) but not in first-degree relatives of schizophrenics (49).

A genetically induced deficiency of platelet MAO activity could produce an increased vulnerability to both chronic schizophrenia and bipolar illness, and this would provide direct evidence of a genetic link between the disorders. Before drawing this conclusion, however, it is necessary to demonstrate that lowered platelet MAO does indeed indicate a genetically increased vulnerability to these disorders, and the studies to date do not prove this. In one study of bipolar patients who themselves had low platelet MAO activity, low platelet MAO activity in relatives was not associated with an increased risk for affective illness (15). Pandey et al. (45) studied relatives of bipolar patients without regard to the patients' MAO status. In 10 relatives with either bipolar I or alcoholism, platelet MAO activity was lower than that of controls. It is hard to accept this as evidence for reduced MAO as a risk factor for three reasons: Alcoholism may be an independent disorder in relatives (39), the authors do not specify how many bipolar relatives there are, and the original patients were not examined for enzyme activity.

In a study with schizophrenics and their relatives, Propping and Friedl (49) found six relatives with "psychological abnormalities" but not reduced MAO, which they interpret along with their other results to indicate that reduced MAO does not predict risk in schizophrenia pedigrees. While low platelet MAO activity may be associated with both schizophrenia and mania, it cannot now be considered a genetic risk factor linking the illnesses and may represent secondary effects of illness or drug treatment.

For alcoholism, on the other hand, Sullivan et al. (57) have shown that patients have reduced mean MAO activity and that relatives of patients who have a psychiatric history have reduced MAO activity, on the average, as compared with relatives who do not have a psychiatric history. This is suggestive, but the psychiatric disorders in the relatives are again not clearly defined. The question of secondary effects of alcoholism on MAO has not been explored. In both this study and the study of Pandey et al. (45)

there is a great deal of overlap in enzyme values between ill and well relatives, so the predictive power of MAO activity would be limited even if one were to accept the findings.

Coursey and Buchsbaum (7) developed a strategy for screening the population for biological markers of vulnerability and looking for psychiatric illness in persons with the marker or in their relatives. Their preliminary results with platelet MAO are described in this volume. Persons fitting diagnostic criteria for the major psychiatric illnesses (schizophrenia and major affective illness) have not been picked out of the population tested with this strategy.

To summarize, reduced platelet MAO activity is found in chronic schizophrenia, bipolar manic-depressive illness, and alcoholism, in some but not all studies. Reduced MAO activity is not established as a predictor of increased risk for any of the major psychiatric disorders in the population as a whole or within pedigrees. Basic questions on the mode of inheritance of MAO activity and its possible reduction as a secondary effect of psychiatric illness or exposure to drugs and toxic agents remain to be answered.

Other Biological Risk Factors in Schizophrenia

Serum creatine phosphokinase (CPK) has been studied extensively by Meltzer and his colleagues (31,32), and they have found that there are elevated levels of this enzyme during the course of hospitalization in many patients with affective psychoses and in many with schizophrenic psychoses, but not in disturbed nonpsychotic psychiatric patients. They also found abnormal muscle biopsies and increased axonal branching of the motor neuron in a high percentage of patients with psychoses of either type. Each of these abnormalities was found to a greater extent among the first-degree relatives of the patients than among controls. The increased psychiatric vulnerability of the relatives who have this neuromuscular abnormality or CPK elevation has not yet been demonstrated. A review of this and other biological factors that may be associated with schizophrenia has recently appeared (33). No factor has been successfully related to genetic transmission of the illness.

Other Risk Factors in Affective Disorders

Recently attention has focused on Lithium transport in the erythrocyte as a possible marker of a membrane defect associated with affective illness (34). Bipolar patients tend to accumulate more lithium intracellularly, apparently because of a defective lithium-sodium counterflow system that normally exchanges intracellular and extracellular sodium, as reviewed elsewhere (44). Dorus et al. (10) studied relatives of bipolar patients, finding that relatives with a history of major or minor affective illness had a higher mean intracellular/extracellular lithium ratio than normal relatives or normal controls. This suggests that the altered transport system contributes to vulnerability. However, the probands (patients introducing the pedigrees) were not examined, and there is a great deal of overlap between ill and well relatives. Replication has not yet been reported.

Except for these variables, there are currently, in my opinion, no promising candidates for biological vulnerability markers to affective disorder with pedigree and population data, as reviewed elsewhere (18).

CHROMOSOMAL LINKAGE AND ASSOCIATION MARKERS

Generally, chromosomal linkage of a marker to an illness implies linkage equilibrium, so that, if there are two marker alleles **A** and **a**, an equal number of pedigrees will be found with **A** persons tending to be ill and **a** persons ill as the reverse type of pedigree. Within pedigrees, an association between marker and illness would be evident, but in the population as a whole there would be no association.

Human leukocyte antigens (HLA) have been related to several disorders by the finding that persons with an illness have a particular HLA type and that the illness is transmitted with that HLA type within pedigrees. This represents linkage disequilibrium, and the HLA type would be associated with illness in the population.

HLA associations with BP illness have been reported but not replicated (2,59) and linkage of bipolar illness to HLA has been excluded (59). HLA associations with schizophrenia have been reported, but, as in bipolar illness, the various reports have not replicated each other. Increased frequency in schizophrenics of HLA-A28 in Czechoslovakia and HLA-A9 in Sweden satisfied statistically rigorous criteria for HLA association by taking into account the number of antigens tested. However, these two findings may be incompatible with each other. Pedigree linkage studies of HLA in schizophrenia have not been reported.

Schizoaffective disorder and bipolar illness have both been reported to be linked to red-green color blindness (an X-chromosome marker) in several, but not all, pedigrees of schizoaffective probands (1,35). In these pedigrees, nearly all of the affected persons are bipolar or unipolar, and schizophrenia does not appear, suggesting that the schizoaffective disorder is a form of the color-blindness-linked bipolar affective disorder previously described (35,36). However, the existence of bipolar illness closely linked to color blindness was not replicated in a recent series of informative pedigrees, in which close linkage is clearly excluded between red-green color blindness and bipolar illness (19). It has been suggested that these results only appear to be incompatible with each other and that there is genetic heterogeneity of BP illness, so that some cases are linked to color blindness and some are not. This explanation does not fit the data from the two reported series from the eastern United States (19,36), since **within** each series there is no heterogeneity among pedigrees; one series is homogeneous for no linkage, the other for close linkage (using the test of Morton (40)). In a recent series (37) in Brussels, Belgium, there did appear to be heterogeneity, but the problem of conflicting results among the other series using virtually the same methodology remains unresolved. Other issues concerning linkage of BP illness to X-chromosome markers have been reviewed elsewhere (13).

Studies of other marker loci have not consistently demonstrated their linkage or association with bipolar (or schizoaffective) illness. Linkage of Xg to bipolar illness was reported by Mendlewicz and Fleiss (36) but not found by Leckman et al. (27). Possible linkage of depression spectrum disorder to the α-haptoglobin or C3 linkage markers has been suggested (58).

PREVENTIVE APPLICATIONS OF CURRENT CLINICAL GENETIC KNOWLEDGE[3]

For the major psychiatric disorders discussed above, family studies show elevated risk of illness in relatives of known patients as compared with the risk in the population at large. These risks can be translated into a heritability statistic (11) which indicates that, using a multifactorial model of transmission, vulnerability to these illnesses is

highly heritable. In this context, heritability is not a demonstration that these disorders are in fact genetic, but rather it is a statement that within the population studied the major contribution to diagnostic variance is familial. That is, a limited number of families within the population account for the greatest part of population morbidity; the individuals within these families are at particularly high risk for major psychiatric illness; and these individuals can be identified through being relatives of known patients. These implications can be applied to the problem of preventive psychiatry in such a population.

Epidemiologic population surveys suggest that significant amounts of untreated psychiatric disability may exist in the general population (29). An important public health goal is to locate the persons with psychiatric disability who can benefit from available treatment. The traditional approach of community psychiatry (67) is to relate the provision of consultation and treatment service through existing social structures, offering consultation and support through schools and neighborhood centers in areas of social distress and to residents of the same household as known patients. The underlying model is of a population in which an individual's predictable risk of psychiatric illness is a function of the status of groups in which he is involved and of observable life stresses which produce crises, including disturbing life events and social conditions. Stresses are often distributed according to the geographic location of segments of the population, leading to provision of services according to area of residence (catchment area).

This approach is appropriate for disorders such as drug abuse, which follow the classic epidemiologic model of the spread of a disease within a geographically defined community at risk. An approach to casefinding and treatment engagement based on a genetic risk of illness for affective disorders and schizophrenia would differ in these ways: (1) Services and the search for new cases are family oriented rather than locality oriented. Relatives are sought outside the usual interactional range of the patients, including persons who are distantly related and persons who live at great geographic distance from the patient. (2) Lifetime diagnostic history, rather than current life stress, is the major clinical focus of attention. In addition to the truism that persons who have suffered episodes of major psychiatric illness in the past are likely to have a recurrence in the future, vulnerability may also be suggested by the spectra of mild forms of psychiatric illness appearing in families with schizophrenia and with affective illness. For example, a young adult with a history of cyclothymic personality or minor depression who is closely related to a manic-depressive patient may be at increased risk for development of severe affective illness. Secondary prevention (early identification of illness and entry into treatment) is the principal goal of this approach. We would not attempt primary prevention by manipulation of social and interactional environment, since there is no evidence that this would have an effect on the lifetime morbid risk of the major psychiatric illnesses. In some instances, primary prevention may be attempted by genetic counseling.

This approach is not offered as a substitute for clinics and hospitals that serve the population living nearby. It is proposed as a way of identifying and bringing into treatment persons at increased risk for the major psychiatric disorders who might otherwise have a delayed entry into treatment or might avoid treatment during long periods of time when treatment is needed. This proposal's utility could be tested by rigorous study of future applications.

As an example of the potential of this approach, consider our findings in 86 bipolar manic-depressive patients studied at NIMH (table 4). There are 405 living first-degree relatives (parents, sibs, and children) over 14 years of age. Six and one-tenth percent of

Table 4. Illness in first degree relatives of 86 bipolar-I patients, by percent. Reprinted with permission from (16), Copyright 1979, Pergamon Press, Ltd.

		Ill	Alive And Ill	Alive And Ill And Untreated	No Information About Treatment
Affective disorders	Bipolar I and Bipolar II	5.9	6.1	1.2	0.2
	Unipolar	10.4	11.1	2.7	1.0
	Minor depression	5.0	5.7	2.0	1.2
	Cyclothymic	2.1	2.8	1.0	0.5
	Depressive personality	1.8	1.7	1.0	0.5
Behavioral disorders	Sociopathy, drug abuse, alcoholism, sexual deviation	5.2	4.9	2.0	1.7
Minor emotional disorders	Obsessive compulsive disorder, generalized anxiety disorder, panic disorder, Briquet's disorder, other psychiatric disorder without hospitalization	1.5	2.0	0.5	2.0
Major disorders	Schizophrenia, schizoaffective disorder, unspecified functional psychosis, other psychiatric disorder with hospitalization	2.3	1.5	0.2	0.7

NOTE: There are 405 living and 105 dead first-degree relatives. Percentage ill not corrected for age.

these relatives have a lifetime diagnosis of bipolar disorder, and 11.1 percent have the diagnosis of unipolar (these figures are compatible with those in the literature (14,18)). Only 33 of the 86 patients had no family history of unipolar illness, bipolar illness, or other major emotional disorder (as defined in table 1). Of the ill relatives, 21 percent were known not to have been treated. Other psychiatric disorders are found with increased prevalence in families of bipolar individuals, and similar proportions of these disorders are untreated, including behavioral disorders (sociopathy, alcoholism, drug abuse) and other major psychiatric illness (schizophrenia, schizoaffective disorder, and undiagnosed psychosis).

These data demonstrate that family-study methods enable identification and location of relatives of patients with illness, including the significant proportion of relatives who are untreated. The yield of ill persons from these procedures is much greater than the population prevalence, so the procedure is much more efficient than a population survey.

Large pedigrees in which many persons in each generation are ill with major affective illness are well known to every researcher in psychiatric genetics, particularly those of us involved in studies of linkage to genetic markers. These pedigrees may account for a substantial proportion of affective disorders in the population, although a precise estimate of the proportion is not possible if, as seems reasonable, they represent families in which special risk factors are present. In any case, they are a rich source of new persons with affective disorders, many of whom are untreated.

Large pedigrees with many ill members are uncovered only by family-study procedures. Our experience in very large pedigrees, even when families are close-knit and found in one region, is that no one family member has all the information on who is ill in the pedigree and who is well. Only patient and persistent professional effort will uncover the many cases of illness in these pedigrees. With the development of national and regional programs of mental health centers in many countries, networks of care-giving facilities and knowledge of large pedigrees will gradually develop, allowing efficient use of preventive efforts in widely dispersed pedigrees.

To implement this goal, I advocate that family-study casefinding programs be added as a separate function to community mental health centers and other programs providing psychiatric care to defined populations. Separate funds for staffing this function and for travel to examine geographically distant relatives are required. The operational goal of each program would be to examine all first-degree relatives and to continue with examination of second-degree relatives where illness is present according to history. Despite the lack of biological or linkage markers of vulnerability, clinical approaches based on investigative procedures used in family and population studies offer attractive preventive opportunities.

Advancement of the epidemiology of genetic risk factors in psychiatric illness requires epidemiologic investigation of pertinent biological characteristics in the population and in pedigrees of patients.

NOTES

1. For example, serum cholesterol and the cell surface receptor for cholesterol are known to be related to genetic vulnerability to atherosclerosis and serve as powerful epidemiologic risk indices.

2. In this discussion, lifetime risk is the probability that a person will ever have a disorder, adjusted to the age structure of the population considered. Lifetime prevalence is the proportion of the living population in which the disorder has been diagnosed.

3. Much of this discussion is taken from our previous publication (16).

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DISCUSSION

Dr. Garmezy: How did you get your diagnoses?

Dr. Gershon: We examined living relatives of the patients ourselves. By-and-large, these were double-blind, face-to-face interviews. We also obtained treatment records and did family histories on each person interviewed and on dead relatives for whom the interviewee could sign a records release form. We did telephone interviews on a relatively small percentage that we could not see. About one-third of the relatives have a diagnosis based on family history and medical records only. These are lifetime diagnoses.

Dr. Garmezy: Did you have a large refusal-to-participate rate?

Dr. Gershon: I would guess that our refusal rate is about 10 percent. We go to great lengths to secure consent.

Dr. Gruenberg: You emphasized the importance of markers. You say that, if colorblindness and bipolar psychosis were near together on the x-chromosome, it would have enormous implications for further research. Could you elaborate?

Dr. Gershon: By identifying the marker on the x-chromosome, you can trace the gene for bipolar illness to different persons. You would know that this sibling is at risk and that sibling is not, so you could rule out many risk factors when you found them in both siblings.

Dr. Guze: If you wanted to see whether losing a mother early in life had an effect, you should study people who have a marker indicating an increased likelihood of the genotype.

Dr. Fleiss: I want to express a concern about your plan of intervention. There are ethical implications and possible invasion of privacy. You knock on a door out in California of a relative of somebody diagnosed here in Washington. You say, "You are sick and I have to treat you." Now this is secondary prevention, and it is none of your business until the individual comes for help.

Dr. Gershon: I do not think that is the case. I went to the person and said, "As part of our study of your relative, Joe Smith, who has consented to my letting you know about his illness, we are studying his relatives. We are interested in seeing which relatives are ill, which are well, because we are looking for ways to differentiate between them. Could we possibly see you?"

If I find that he has had minor depression, then I will say to him, "I have reason to suspect that you might be at higher risk for manic depressive illness than you may have thought earlier, and I would advise you to keep in touch with me."

Dr. Marks: In which psychiatric syndromes do you think the evidence of genetic transmission is sufficiently strong to warrant genetic counseling?

Dr. Gershon: Manic depressive and related illnesses, schizophrenia, and, in some adoption situations, sociopathy and alcoholism. About whether or not people should reproduce, one would explain risks but would give specific counsel only in certain very restricted cases. To illustrate such a case, if two chronic schizophrenics came to me and said, "We are interested in getting married and having children. How high is the risk to our offspring?"

I would say to them, to the extent that clinically they could bear the information, "Your risk is about 40 percent if you have children with each other and considerably less if you marry someone else."

THE BIOLOGICAL HIGH-RISK RESEARCH STRATEGY: A REVIEW OF RECENT STUDIES

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INTRODUCTION

The traditional research strategy in biological psychiatry has been first to carefully define a set of patients on the basis of a diagnostic category. Thus, the psychiatric diagnosis becomes the independent variable. The biological factor, even though it is hypothesized to be etiologically significant, then becomes the dependent variable. Because of both the difficulty in establishing mutually acceptable and reliable diagnoses (9, 23) and the widely held assumption of 'biological heterogeneity (e.g., 3, 12) in the etiology of the major cognitive and affective disorders, we have been urging the adoption of a biological high-risk model, where the independent variable is a homogeneous biological factor and the dependent variables are psychological traits, behaviors, symptoms, and diagnoses (7, 12, 16). Such a method tests the power of the biological variable by seeking to demonstrate whether deviant biology is significantly related either to increased prevalence of a predicted mental disease or to some normal or pathological behavior, affect, or cognition. The advantages and disadvantages of this method have been discussed elsewhere (12, 16).

Using this research strategy, the simplest assumption is that a single biological factor is of sufficient strength to cause statistically noticeable differences in the prevalence of a disorder or symptoms between biologically deviant and normal samples. The first section of the paper will survey studies where the independent variable is primarily a single biological factor. But, such a single factor model is a gross oversimplification of mental disorders. Severe mental disorders are more realistically the result of interacting biological and/or environmental variables. The second section of this paper will review these more complex biological high-risk studies and present some of our speculative conclusions and recommendations, especially with respect to the relationship of monoamine oxidase with schizophrenia and affective disorders.

SINGLE FACTOR MODELS

A wide range of biological variables have differentiated psychiatrically diagnosed groups from controls, but a more limited number have been used in risk studies. Four variables for which there is this kind of data available will be discussed: (1) Skin Conductance Response (SCR), (2) the Continuous Performance Task (CPT) which is a measure of attention, (3) Smooth pursuit eyetracking, and (4) blood platelet monoamine oxidase (MAO) activity. We have elsewhere (8) delineated what we felt are the prerequisites that a biological variable ought to display before being used in this type of research; the four under discussion meet these criteria to an acceptable extent.

It should be noted that most biological variables are normally distributed. Because of this continuum, it is not unreasonable that the psychological expression of the biology would also be a continuum. The more general research strategy, of which the biological high-risk method is a special case, is the simple population correlational study. For these correlational studies to be psychiatrically useful, however, they need to include traits, behaviors, and affects which vary continuously from severe illness into the normal range (15) or at least variables that are clinically or theoretically meaningful to the disorder. Where such information is available, we will first present these normal correlational data.

Skin Conductance Response

The biological variable chosen for this first biological high-risk study was drawn from the reports in the work of Gruzelier and Venables (e.g., 26) of a bimodal distribution of responsivity of skin conductance in a heterogeneous group of schizophrenics and from Mednick's longitudinal high-risk research (e.g., 35). (This material is reviewed in 51.) The resulting Mauritian study (2,36) used children who had hyperresponsive or hyporesponsive patterns of electrodermal activity to define the high-risk groups. From the initial screening of 1,800 3-year-old children, 144 deviant and 56 with normal galvanic skin response (GSR) were selected. The first followup took place at age 6 when the children were observed in a standardized play situation. There were complex interactions between GSR and nursery-versus-community placement on "constructive play," "watching," and "positive interaction" which seemed generally in accord with what might be expected, given the psychophysiology. The children are now 10 years old, and further studies are awaited.

Continuous Performance Task (CPT)

Disorders of attention are prominent experimental laboratory findings in both childhood hyperactivity (21) and schizophrenia (e.g., 24, 50). The CPT (43) provides a measure of vigilance or sustained attention which differentiates normals from hyperactive children (21), from long-term remitted schizophrenics (33, 54), and from children of schizophrenics (44). Similarly, Asarnow et al. (1), DeAmicis and Cromwell (18), Herman et al. (29), and Wood and Cook (55) found attentional deficits on other attention tasks in children or siblings of schizophrenics. Thus, in a sample of individuals with attentional deficits on the CPT, we might find more individuals with symptoms of schizophrenia and other forms of psychopathology or with a history of childhood hyperactivity than among individuals without such a deficit.

Four hundred college males were screened on the CPT, and individuals with good and poor attention (the upper and lower 5 percent of the CPT-score distribution) were compared on multiple measures of psychiatric disturbance, cognition, and psychophysiological function. The attention dysfunction group had a higher incidence of symptoms of hyperactivity both as children and as adults but no higher incidence of other psychopathology as assessed with both the Schedule for Affective Disorders and Schizophrenia structured interview (22) or the MMPI. Cognitive differences, including WAIS subtests, the Stroop test, reaction time, and evoked potentials, substantiated an attention-dysfunction syndrome. Thus, attentional dysfunction in young adults seems more closely linked to hyperactivity than to current psychopathology. These results provide some support for the new DSM-III diagnosis Attention Deficit Disorder as a replacement for childhood hyperactivity.

Smooth Pursuit Eyetracking

There is an increasing body of literature (30) which reports poor smooth pursuit eyetracking in psychiatric patients and their relatives. Iacono and Lykken (31) provide some data on the correlation between eyetracking deficits and psychological variables in 32 pairs of normal adult monozygotic twins. Of special interest are the correlations with scales measuring psychoticism and absorption. Subjects who scored high on psychoticism tended to have longer saccadic eye movement latencies and performed especially poorly when following high-frequency sinusoidal targets. High scorers on absorption, which characterizes people who seek and enjoy imaginative experiences, tended to be good smooth pursuit trackers, especially at slower target speeds.

We have run several pilot studies on eyetracking using subjects drawn from our prior high-risk studies. In one sample, some support for the Iacono and Lykken results was obtained. The number of velocity arrests correlated significantly with MMPI scales. Poor eyetracking was significantly related to elevations on the Paranoia scale, Hypochondriasis scale, and the Psychasthenia, Schizophrenia, and Social Introversion scales.

In a second sample of 9 poor and 81 good eyetrackers, the poor eyetrackers had higher penetration responses and less human movement responses on the Rorschach, poorer self-concept on the Tennessee Self-Concept Scale, fewer heterosexual contacts, greater introversion on the MMPI, and an increase in Disinhibition scores on the Zuckerman Sensation Seeking Scale. These two pilot studies suggest that poor eyetracking performance may well be related to increase in psychopathology, poorer self-image, and greater social withdrawal.

A large-scale high-risk study of eyetracking under the direction of Dr. Larry Siever is now in progress at NIMH.

Blood Platelet MAO Activity

There have been more studies of the psychological correlates of MAO in normals than with the other three biological variables. The dimensions that have been most replicated seem related to the person's disposition to seek stimulation in the outside environment. Examples of this theme include the association of low MAO values with high scores on the Sensation Seeking Scale (37, 45), and with increased social interaction in both humans (14) and monkeys (42), cigarette usage (14, 32) as well as drug usage (14),

greater activity and play in monkeys (42), a tendency toward more stimulating leisure-time activities in man (45), and psychopathic traits and legal convictions (7).

In the first MAO high-risk study (14), we screened 375 college students and selected the top and bottom 10 percent of the platelet MAO distribution for both males and females. A structured interview yielded the following major findings: (1) Both the male and female low MAO groups were more social on a variety of measures. (2) More subjects in both male and female low MAO groups had seen a psychiatrist. (3) Significantly more low MAO males had been convicted of crimes than high MAO subjects. (4) The low MAO males smoked significantly more cigarettes and either had used or were using significantly more stimulants, hallucinogens, and depressants, as well as a wider variety of these drugs. (5) Among the relatives of low MAO males (mother, father, brothers, sisters, aunts, uncles, and grandparents), there were significantly more individuals who had attempted or completed suicide than among relatives of high MAO males. The four completed suicides occurred only among low MAO relatives. MMPI results also indicated greater psychopathology among low MAO subjects. Using Peterson's signs (40) for a psychotic MMPI profile (schizophrenia plus three other scales elevated more than two standard deviations), eight of the low MAO Ss of both sexes and only one of the high MAO subjects had such a profile (significant difference).

Our general conclusion from this study with respect to MAO's relationship to affective disorders versus schizophrenia was that, although most of the findings were somewhat equivocal, nevertheless, a stronger case could be made for affective disorder type of symptoms, especially in light of the strong findings for increased involvement in social relations and activities.

We reinterviewed these students (17) 2 years after completion of these initial studies and found that the same pattern of results was continuing. The low MAO subjects reported more job instability and smoked significantly more cigarettes than the high MAO subjects. Moreover, the low MAO males had fallen about half a year behind their high MAO counterparts in school. While the low MAO subjects reported no significant decline in their own mental health status during this period, significantly more low MAO male subjects did report current mental health problems in their families, especially depression, alcoholism, and suicide attempts, as well as significantly more mental health interventions among family members, such as psychiatric visits, prescription of psychotropic medication, and psychiatric hospitalization.

Because of these reports of affective-type disorders among the relatives of our subjects, we interviewed the parents (41) of our MAO probands with the SADS (22). Results showed generally positive and significant correlations between parents' and children's MAO levels, significantly greater rates of "high MAO-related disorders" (major or minor depression, depressive personality) in parents and relatives of high MAO probands, and greater rates of "low MAO-related disorders" and symptoms (bipolar affective disorders, alcoholism, and antisocial personality, but not schizophrenia) in parents and relatives of low probands.

THE DOUBLE FACTOR MODEL

Following up the affective versus schizophrenia relationship with MAO, we will examine in this section the power of multiple biological criteria in predicting mental

illness: MAO + lithium transport characteristics of cells, MAO + evoked potentials, and MAO + DBH. We will also present a biology-stress high-risk study.

MAO and Lithium Transport Characteristics

Lithium is widely used in the treatment of patients with affective disorders. Like MAO, the lithium transport in the red blood cell (assessed as the in vitro ratio of red cell to plasma lithium concentration) may be important in the pathophysiology of some psychiatric disorders. The "Li" ratio is to some extent under genetic control (20); and in some but not all studies, patients with affective disorders have higher Li ratios than normal controls (see 46). In a study of the families of patients with bipolar affective illness, Dorus et al. (19) found that all relatives having both low MAO and high Li ratio had a history of affective illness, the other combinations having a lower and equal incidence.

Shaughnessy et al. (46) extended this research into a sample of psychiatrically normal adult women, including women who were in the upper and lower 30 percent of the Li distribution and the upper and lower 40 percent of the MAO distribution. They found a unique constellation of personality traits on the Clinical Analysis Questionnaire when the two variables were considered simultaneously. While none of the four groups was significantly similar to previous clinical profiles, the low MAO groups were significantly more similar to the chronic schizophrenic and manic-depressive, manic-type groups than were the other three groups. The lack of truly extreme groups in this biological high-risk study may have reduced the strength of these findings.

MAO and Evoked Potentials

Most of the studies using the double-factor model have combined MAO and evoked potentials in the electroencephalogram. This choice was made because it might help clarify MAO's relationship to schizophrenia and affective disorders. This reasoning was based on studies (see review by Buchsbaum, 6) which found that schizophrenics generally have smaller average evoked potentials (EPs), while individuals with bipolar affective disorders generally display larger EPs (5) than appropriate controls. These differences between bipolars and schizophrenics seemed especially marked at high-stimulus intensities (6). More specifically, in all of the studies reported below, individuals in both low and high MAO groups were further subdivided, depending on whether EP amplitude tended to increase rapidly (augmenters) or minimally (reducers) with increasing stimulus intensity.

The first set of studies to be reviewed here used diagnoses as the dependent variable. The impetus for these studies was the finding in our college sample (28) that psychiatric symptomatology based on blind individual profile analyses of MMPIs appeared to cluster in low MAO-EP augmenting and high MAO-EP reducing groups. A new sample (28) of 385 college males were then recruited to cross-validate this finding. Because we wanted to increase the prevalence of psychiatric disturbance in our sample, we selected an index sample of everyone with a score on any clinical MMPI scale over four standard deviations above the mean for adult males in the general population. We also selected a control group which had all MMPI scale elevations within normal limits. In the index group, 20 of the 35 Ss met the RDC for at least one affective disorder, and only 3 of the 27 controls met the RDC for any of these affective diagnoses. No cases of schizophrenia and few other diagnoses other than affective disorders were found.

Platelet MAO activity was assayed, and the middle third of the distribution was omitted from further study. Thirty-eight subjects met the criteria for inclusion in either the low or the high MAO groups. These were then dichotomized into augmenting and reducing. Here, too, the disorders fell predominantly into the low MAO augmenting and high MAO reducing categories. Fifty percent (6/12) of the low MAO augmenters, 0 percent of the low MAO reducers (0/12), 20 percent of the high MAO augmenters (1/5), and 55 percent of high MAO reducers (5/9) received diagnoses. Overall, 52 percent of the low MAO augmenters and high MAO reducer groups met the RDC for any diagnostic category, whereas only 5 percent of the other two groups were so diagnosed ($p < .005$, chi-square).

Seventeen to 20 months later, 32 of these 38 subjects were reinterviewed (27) using the latest SADS-L probes. At the followup, the distribution of Ss meeting the RDC for a new affective episode during the interval followed a similar pattern: low MAO augmenters 83 percent (10/12), low MAO reducers 28 percent (2/7), high MAO augmenters 0 percent (0/4), and high MAO reducers 33 percent (3/9). A second analysis concerned the 27 cases that did not meet the RDC for major depression at the original interview. Of these cases, six did meet the RDC for major depression at the followup interview. All six had low MAO (Fisher exact test, $p < 0.027$), and four were augmenters ($p < 0.05$ by chi-square).

Notice that this last study and its followup do not clearly address the schizophrenia risk issue since no schizophrenic diagnoses were found in the original sample. Also, for this reason, we would not expect any diagnoses in the low MAO reducer category since this is where schizophrenic-type disorders would be expected to fall. However, it does demonstrate a relationship between affective disorders and low MAO augmenting and high MAO reducing.

Some symptoms often associated with affective disorders also demonstrate this interesting interaction effect. For instance, in the original college sample, among the females, there were significantly more low MAO augmenting subjects (8/12) who had alcoholic relatives than low MAO reducing subjects (1/6) ($p < .05$, Fisher test). Another symptomatic behavior is suicide. Here, 6 of the 24 low MAO augmenters had relatives who had attempted suicide, while there were none among the low MAO reducers ($p < .05$, Fisher's test) and none in the high MAO group ($p < .025$). We attempted to cross-validate this study with a group of 79 inpatients (10). Using the traditional research method, suicide attempters did not have significantly lower MAO activity levels but did have significantly higher EP augmenting than nonattempters. Using the biological high-risk approach, male individuals with low MAO and EP augmenting showed a significantly increased incidence of suicide attempts in comparison with either nonaugmenting low MAO or high MAO patients. In fact, the lower the patient platelet MAO level, the stronger was the relationship between EP and suicide attempts.

A final study (15) explored the psychological characteristics of people who fall in these four categories of risk. To do this we gave an extensive psychological test battery to the original 68 high-risk college students (7). An additional 30 students whose MAO values were near the median were tested in order to have a large enough N to factor analyze the psychological test scores. The 10 resulting factors included those measuring mania-sensation seeking (e.g., Zuckerman's Sensation Seeking scores), general psychopathology (e.g., most MMPI clinical scales), remote associations (e.g., Kent-Rosanoff Word Association Test), accurate perception of stimuli (e.g., Rorschach R+%), and social interaction. Two-way analysis of variance (MAO x EP) yielded the following results.

For the male group alone, the low MAO group had significantly elevated scores on the general psychopathology factor. Also, the interaction effect of MAO and EP was highly significant for the remote associations factor, with the low MAO reducers giving the most remote associations. This low MAO-reducing category contains the subjects hypothesized to be at risk for schizophrenia. Finally, factor nine measuring the accurate perception of stimuli approached significance for the two levels of MAO. This was largely due to the good perception of the low MAO augmenters (the subjects at risk for affective but not schizophrenic disorders).

Among the females, the interaction between MAO and EP was again significant for the remote associations factor. In addition, the differences between high and low MAO females on factor four (sensation seeking and mania) approached significance with the low MAO group means in the predicted hypomanic direction. Finally, the interaction of MAO and EP for general psychopathology also approached significance.

MAO and DBH

Using the double factor model, we have explored subjects who are presumably at high-risk due both to extreme MAO levels and low plasma dopamine-beta-hydroxylase (DBH) levels (11). DBH, like MAO, is a stable enzyme, under genetic control (25, 52), and important in the metabolism of dopamine. Although studies using DBH alone have generally not found reduced levels among schizophrenic patients, nevertheless, since both low MAO and low DBH might lead to central increases in dopamine, subjects with both low MAO and low DBH might be particularly vulnerable to psychotic symptoms.

The dependent variable in this analysis was a central schizophrenic symptom—attentional deficit, which was measured by the Continuous Performance Task and visual and tone evoked potentials under conditions of selective attention and inattention. Among individuals low in both platelet MAO (from the study of Buchsbaum et al. 7) and plasma DBH, attentional performance on both measures was poor in comparison to individuals with high MAO or high DBH levels.

Biological-Environment Model

Our most recent work is a biological-environment high-risk study (32). One hundred seventy-eight adult males from 20 community clubs with widely differing backgrounds were screened on the basis of their MAO values (upper and lower 15 percent plus a middle group) and stress scores (median split). Significantly more subjects from the low MAO groups had seen a psychiatrist or psychologist; they drank more frequently (time since last drink was measured) and smoked more. This last behavior also increased with increasing stress. The high MAO groups also scored significantly higher on two MMPI clinical scales (Hs and Hy). Stress was also significantly related to drug use and to increased incidence of psychiatric problems among the relatives of the subjects. Interestingly, more low MAO subjects reported high stress than the middle and high MAO groups. We are currently investigating whether the types of stress experienced (such as more self-induced stress) differ among the three groups.

CONCLUSIONS

We suggest a few speculative conclusions based on the findings from these high-risk studies, particularly those on MAO, keeping in mind the data from the rest of the literature.

1. MAO alone appears to be a significant but weak variable in explaining psychiatric disorders. Because this is so, it makes sense to undertake studies which combine MAO with other neurochemical, electrophysiological, or cognitive variables which might increase a particular disposition, e.g., toward manic-type behavior, or studies in which MAO may disinhibit some other biological predisposition.

2. Research using a biological high-risk strategy strongly supports the notion that MAO does heighten the likelihood of affective-disorder type of behaviors and affects. This, of course, is bolstered by studies relating low MAO levels to bipolar affective disorders, alcoholism, drug usage, social behaviors, sensation seeking, as well as studies of increased motor activity in animals.

3. The relationship of blood platelet MAO values to an addictive personality needs exploration. This is based on the biological high-risk studies which linked low MAO values to cigarette smoking and drug usage, as well as on the studies of marijuana users (47) and alcoholics (4, 34, 48, 49, 53).

4. Prior studies demonstrating the stability of platelet MAO values in the face of extreme fluctuations in psychiatric symptoms (13, 38, 39), and the low prevalence of disorders found among the biological high-risk subjects support the notion that MAO values are related to a predisposition rather than directly to particular symptoms and disturbed behavior.

5. The relationship of MAO values to chronic schizophrenia needs to be subjected to careful analysis. The fact that no diagnoses of schizophrenic disorders were made in any of the biological high-risk studies (despite platelet MAO values as low or lower than those observed in schizophrenics) suggest that MAO by itself is not directly related to any particular schizophrenic symptom or diagnosis. Alternative pathways relating low MAO values to schizophrenia need to be explored; e.g., do levels of MAO lead a schizophrenia-prone individual to create a stressful life for himself? Do low levels of platelet MAO create a need for heightened stimulation which, in the presence of a nervous system which will not permit adequate external stimulation (as measured by EP reducing), encourages loose associations and hallucinations? Is MAO's relationship to schizophrenia merely an artifact, because MAO predisposes persons to high levels of cigarette smoking and this variable has not been satisfactorily controlled?

6. Finally, methodologically we would urge research psychiatrists to examine the specific psychiatric correlates of MAO and other biological variables, and not to use the very broad diagnostic categories which include a wide variety of symptoms, behaviors, and biologies. Moreover, we would want to encourage multivariate experimental designs which examine several biological factors or both biological and environmental factors together. We hope we have provided a research strategy that makes this possible.

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DISCUSSION

Dr. Raskin: I am curious that this was a sample of college kids who were functioning, I guess, reasonably well in a college setting. Yet you get these wide differences at both extremes.

Dr. Buchsbaum: One of the things we have learned in our studies out in the community is that there is an awful lot of variation in human nature. This is one of the advantages of going out in the community.

Dr. Klein: Have any been diagnosed?

Dr. Buchsbaum: Yes, three were hospitalized for psychiatric reasons. All three had low monoamine oxidase, and no one with high MAO had been hospitalized for psychiatric illness. Two hospitalizations were for suicide attempts and one for problems around drug abuse. That is three out of thirty versus zero out of thirty, which misses significance, so even a cohort of 400 is not enough for this kind of study. That is why we need to tap into epidemiologic studies of the kind Dr. Regier is planning.

Dr. Kramer: Let us look ahead 10 years, as you suggested. Given the information you would generate, and given individuals with these characteristics, what do you recommend be done for them? As I understand it, one of the purposes of detecting risk factors would be to see if you could modify the risk. What would you do?

Dr. Buchsbaum: It depends very much on the information generated. Basic neuroscience research would have to determine the essence of low monoamine oxidase. First, is it really a risk factor, and second, if it is a risk factor, would it help to do something about it? I would not say that we want to adjust monoamine oxidase levels.

DISCUSSION OF DR. GRUENBERG'S PAPER

Dr. Gershon: One focus of the meeting is the catchment area approach to epidemiologic studies. Is that approach appropriate to disorders which are genetically transmitted and in which pedigree studies might be desirable?

Dr. Gruenberg: If you are interested in pedigrees, you need a population where pedigrees are known, and you have to be able to find the relatives, and you have to be able to gain their cooperation. Islands are great for this sort of thing; continents are terrible. You need to study the kind of place people came from, not the typical ecological catchment area which is a place people came to a center of migration.

Dr. Weissman: On the other hand, an ECA study can provide useful information on incidence and prevalence rates in the population. Such information is commonly required in genetic models for comparison with rates in families of probands.

Dr. Kramer: There is a problem of sample size; i.e., the number of persons being studied in the catchment areas. You would have to double the sample size, at least, in the age group 15-44 years to find a large enough number of schizophrenics in an epidemiologic catchment area.

Dr. Weissman: The ECA could also be useful for selecting the proband samples for genetic studies. For example, a genetic-family study of schizophrenics could select cases from a probability sample derived from the community and including schizophrenics who may never have been hospitalized.

Dr. Gruenberg: An ecological catchment area may pose problems of selective migration. If it is a place people came from, the healthier residents may have migrated elsewhere, or the most seriously affected may have gone to a locus of medical care. Twenty years ago these loci were mostly State mental hospitals, and it was fairly easy for the geneticist to trace them. Today, "de-institutionalized" people have often moved to other communities, and the record systems of the hospitals are in disarray.

I would advise caution in using an ECA group of cases for probands and controls for familial aggregation studies; one would have to appraise the feasibility of tracing relatives in a manner which would not be biased with respect to whether the relative had the disorder of interest.

If the disease has a genetic marker or a vulnerability marker, it can be used in case-control studies, and you do not have to follow the pedigrees. In this case, the ECA approach can find out what else is needed in combination with a susceptible genotype.

Dr. Guze: Perhaps we are too conservative about the study of markers. The geographic distribution of the Duffy antigen on red cells led to its recognition as a potential key to the eradication of malaria. Maybe in all these epidemiologic studies we ought to be willing to add a certain cost to do blood types and other relatively easy things.

Dr. Gruenberg: They could freeze a part of the blood samples to reserve for marker questions that emerge 3 or 5 or 10 years later as a result of other research.

Dr. Kramer: In the ECA we have probability samples of the household population as well as of the institutional populations. If we could include a blood sample and a test for MAO inhibitors, they could be put together in a meaningful way with a DIS diagnosis and other information. If we can overcome the problem of obtaining informed consent, I think that the ECA study, combined with the most promising biological markers, would provide a laboratory for studies that could not be done otherwise.

Dr. Marks: While we are discussing markers, perhaps we need to consider psychosocial markers that might be quite cheap to study. And I should also like to ask a question about our goals that has a bearing on the issue of risk factor research versus basic research, if these are seen as antitheses. If our aim is to reduce expenditures on mental disorder while also relieving suffering, would not the prevalence of disorders enter into decisions about priorities of funding? For example, the anxiety-depression group of disorders probably accounts for more consumption of health services than all the other mental problems combined.

Dr. Regier: Yes, I think we have to consider both social cost issues and basic scientific issues. Phenylketonuria is not very prevalent as an illness, but the power of the tools to diagnose and treat it make it almost mandatory to screen for at birth.

IV

INTERACTION AND CONCLUSIONS

WORKING GROUP ON GENETIC, BIOCHEMICAL AND PHYSIOLOGICAL RISK FACTORS

Co-Chairmen: Samuel Guze and Monte Buchsbaum

Both workshops or discussion groups were asked to try to extract from the previous day's discussion those risk factors sufficiently promising to be used in epidemiologic studies. The groups were also asked to consider the type of preliminary or full-scale epidemiologic study needed for each risk factor.

The Biology Workshop stopped short of recommending particular variables but presented well-thought-out criteria for selecting risk factors or potential markers to be used in large-scale epidemiologic studies. A second message was one of tempered enthusiasm toward incorporating biological variables into large-scale mental health epidemiologic studies.

An objection to risk factor research raised by some participants was that the risk factors may become an end in themselves. Others considered it worthwhile to document risk factors as case-finding tools to identify high-risk individuals deserving of longitudinal study or suitable for empirical intervention research. At this stage of knowledge, however, risk factors are most useful as clues to etiology. Efforts should therefore be concentrated on those which appear to be causal or at least, like sex, readily suggesting etiological hypotheses.

The value of intervention even when the cause is unknown was defended by analogy with the 19th century control of cholera, achieved by management of water supplies before the cholera vibrio had been identified. Specific proposals for new interventions on an epidemiologic scale concentrated on benign positive measures, e.g., training children to overcome attentional deficits on the basis of findings in the longitudinal high-risk research on schizophrenia.

One participant warned against preventive intervention efforts that have no chance of success but are attached to an academic study to win financial support or patient cooperation. Even measures such as genetic counseling, aimed at a very limited clientele, were said to be vulnerable on ethical grounds. Reasons for caution include not only insufficient evidence to justify the inevitable trauma or inconvenience to high-risk subjects but even ignorance of whether "corrective" measures may, instead, be detrimental to persons who will become disordered.

Equally diverse views were expressed on the subject of incorporating biological measures in large-scale, mental health epidemiologic research. At one extreme there was disappointment over the failure of the current NIMH-sponsored ECA Program to

include biological measures in the original plans. At the other extreme was the view that worthwhile biological studies cannot be done on such a large scale and with the same methods and could at most piggyback on a random or selected subsample of cases documented in an ECA project. Some participants were eager to take advantage of the ECA program at once, advocating inclusion of markers that interest the staff of the individual ECA projects. They were warned that the ECA funding will not support much more than is already planned. Major initiatives in biological risk factors, if possible at all in the first generation of ECAs, will require independent funding.

The subject of funding led to a discussion of the possibly negative impact of a large program like the ECA plan on career opportunities for young investigators. Large, short-term projects require extra short-term staff. Senior investigators may not be eager to incorporate ambitious marker studies in short-term projects, and without long-term funding prospects the individual young investigator is not encouraged to plan a career in epidemiologic research. These concerns were not seen as peculiar to epidemiology.

Another tangential theme was received more enthusiastically: the need for better communication of new findings in risk factor research. One example of this need is the widespread confusion about what has been learned in the high-risk studies of schizophrenia. This need could be met by regularly scheduled conferences, by periodic, well-focused reviews of risk factors, or by a special newsletter or journal that permitted rapid publication.

Which risk factors are appropriate for a large-scale epidemiologic study? The group did not endorse and would not even attempt to rank the risk factors reviewed by the speakers the previous day. Instead, many additional variables were proposed, ranging from pharmacological challenges to video-tape recorded interviews and collection of babybook data. There was support for collecting data on markers that could have no etiological role but have potential for use as chromosome markers or in defining racial or ethnic subgroups of the population. This would call for frozen blood and tissue samples.

This great catalog of proposals dramatized the need for objective criteria for including any given risk factor or marker. There was very little disagreement about what criteria were appropriate or even about the priorities.

1. **Readiness for epidemiologic use.** Research on a risk factor must already be advanced to the point where application in a large population will be fruitful. A solid groundwork should exist in case-control and small-scale studies, and remaining questions should concern population distributions, frequency of false positives, etc.

2. **Etiological relevance.** A variable should have a confirmed or very plausible relationship to causation of the disorder. Failing this, it should rate very high on the next criterion.

3. **Predictive value.** There should be a body of empirical evidence for an association of the variable with mental disorders. This is more relative than are criteria (1) and (2), both sensitivity and specificity being measurable on quantitative scales.

4. **Reliability of measurement.** Methods or tests are needed that have relatively small measurement error.

5. **Stability.** The variable should mark a trait rather than a state. At least, it should be stable in an individual from day to day.

6. **Low burden to the subject.** Measurement of the variable should not be too painful or impose significant risk to the patient or invade privacy.

7. **Low cost.** Measurement should not require unduly elaborate equipment, specialized analysis, expensive reagents, or time-consuming procedures.

8. **Availability on all subjects.** In general, measurement should be possible at any time and place without too much dependence on skillful cooperation by the subject.

9. **Promise of scientific payoff.** Epidemiologic study of the variable should be expected to produce useful new information, perhaps to aid in diagnosis or therapy or simply to exclude its relation to disorder.

10. **Familial occurrence.** This and the next criterion should not be required, but genetic traits and family environment present rich opportunities for causal analysis.

11. **Promise as a modifiable cause.** Beyond etiological relevance, modifiability would enhance the value of a risk factor for preventive intervention.

In discussion of the criteria for including individual risk factors, it became clear that even such a well-studied variable as platelet MAO may not be ready for application in large populations. Given the inadequately understood interaction among risk factors, one cannot say just what **cluster** of variables should be measured together. Such hesitancy to include variables was criticized on the grounds that any genuine risk factor should affect relative risks when measured alone in a large study, and very few variables are expected to have a constant association with any mental disorder.

The difficulty of applying these criteria, particularly the quantitative ones (3 to 9), raised the question of who should make such decisions. Some said they would be uncomfortable with committee-directed, targeted research because it tends to inhibit innovation. Others pointed out that investigator-initiated projects often compete for scarce funds, and a conservative proposal is more likely to win than one that casts a wide net. They all recognized the superior efficiency of direction by a committee for large-scale epidemiologic research projects. Given the realities of Federal funding of such projects, the group urged that committees that choose risk factors for study should be attuned to the latest technical knowledge and should also strive to maintain flexibility among different collaborating investigators.

WORKING GROUP ON PSYCHOLOGICAL AND SOCIO-ENVIRONMENTAL RISK FACTORS

Co-Chairmen: Norman Garmezy and Myrna Weissman

This discussion group spent a considerable amount of time reexamining some of the basic and general issues underlying the goals of the meeting: definition of a risk factor, calculation of relative and attributable risks, and design of current and future epidemiologic studies.

Like the other group, they reviewed a much wider range of risk factors than those mentioned the previous day in the formal papers. These were entered, generally without challenge, in a table resembling Eaton's table 1, with both dimensions of the table allowed to grow by addition of new categories and by subdivision of categories already entered. Needless to say, this approach produced a very large array of factor-by-diagnosis cells, which finally had to be trimmed drastically. The need for a meaningful framework was apparent. Some wanted to concentrate on modifiable risk factors, but others demurred.

In constructing and in trimming the table, a number of considerations were raised, beyond the issues treated in the formal papers. First was the importance of including children in epidemiologic research. Behavior disorders and learning problems are much more frequent in children than major psychiatric disorders are in adults, and therefore would yield more significant findings in a population sample as small as 4,000. More important, these conditions in children may be risk factors for adult disorders, and they certainly raise questions of need for various types of support to the family. Personality disorders, anxiety, and depression all seem to have some roots in early development or in the childhood milieu. Modifiable risk factors should first be sought in child studies. A prospective study starting with children would yield much better data than the available retrospective studies and would also lend itself to limited intervention trials.

Coping skills are recognized to be very important as a modifying variable which protects against negative life events. But coping skills blend into social competence, current social functioning, and subjective well-being, on the one hand, and blend into IQ, on the other hand. Social skills are closely related to social support and the social network. Measured at the time of mental disorder, poor coping and poor social skills are likely to reflect consequences of, rather than risk factors for, mental disorders, so that they need to be measured before onset. Whether deficient coping skills are, in fact, risk factors for mental disorder and how they interact with other risk factors in the emergence of disorders are points of ignorance. Although this is an area in which

intervention appears to be feasible, it is first necessary to determine how coping skills can be taught successfully at various age levels—areas requiring additional health education research.

A record of life events may provide much more information than simple measures of stress. Carried back to childhood, life events would usually include early loss of a parent, family disruption, family history of mental disorder, school failures, and teenage pregnancy. Recent life events may include illness, serious accidents, positive events with protective potential, geographic mobility or instability, loss of employment, family problems including behavior or health problems in one's children, and loss of spouse. As with many other risk factors, there are unsolved problems in the interpretation of life-events data.

The problems of sample size and design were discussed repeatedly. Onset of schizophrenia and especially of bipolar affective disorder will occur infrequently in the 1-year interval to be studied in current Epidemiologic Catchment Area projects, even after combining samples. Some groups can be intentionally oversampled, such as the aged. Special efforts would be needed to measure the localized influence of high crime rates or drug traffic, as distinct from lower social class per se.

Risk factors in the psychosocial sphere need to be chosen in consultation with biological scientists to assure collection of all relevant, essential information. Ultimately, the study of correlations and interactions within and between the two spheres will be necessary and should be reflected in the data-collection stage.

In trimming the list of risk factors to be recommended, the chairpersons listed the following guidelines for including and defining a variable: (1) importance of the variable in terms of magnitude of exposure and in terms, when known, of relative or attributable risks; (2) reliability of measurement; (3) feasibility for a community survey; and (4) specificity for one or more major mental disorders. Participants repeatedly raised the issue of modifiability as a criterion, but this was rejected as an absolute requirement.

These criteria were not, indeed could not be, applied in a uniform manner, and some of the recommended variables remained controversial. Other variables listed below hardly need mention because they would always be included, but their specificity for particular mental disorders may be at issue. Very few variables were clearly ruled in or out, so that the list is not determinate. It does not take account of specificity or of importance in terms of patient numbers, which in many instances are arguable matters.

1. Age
2. Sex
3. Race
4. Religion
5. Marital status
6. Ethnic identification
7. Urban/rural residence and city size
8. Time and season of interview

9. Social class, separating education and occupation

10. Physical health; chronic diseases, current health status, recent accidents, and any head injuries

11. Social and coping skills and current social functioning

12. Intelligence

13. Sibship size and birh order in family of orientation

14. Age at death of parents

15. History of family disruption, foster care

16. Problems with one's children

17. Family history of psychiatric disorder, for testing social as well as genetic hypotheses

18. Life events

19. Living arrangements: household composition and roles.

20. Social support; availability of a confidant

LARGE-GROUP DISCUSSION

Following summarization of the two working sessions by Dr. Buchsbaum and Dr. Weissman, there was a lively exchange of ideas and arguments. The following summary includes some remarks that were invited by Dr. Klerman in his concluding statement. Some of the discussion is represented not in this summary but in the final chapter, the Editors' Summary.

SHOULD THE STUDY OF SOME RISK FACTORS BE ADDED TO CURRENT EPIDEMIOLOGIC RESEARCH PROGRAMS?

This issue was raised in various forms by participants and by staff: Are risk factor items an appropriate part of large-scale epidemiologic studies? Is risk factor research important to add to current programs, such as the ECA, to capitalize on the opportunity provided? Are any risk factors well enough documented to warrant inclusion at this time?

The most negative views were those of Dr. Kety: "Why not justify the ECA Program for its own value, which is to ascertain the prevalence of a variety of mental disorders in the community, and let it go at that?" He doubted that any useful new information relevant to etiology or prevention would come out of either the biological or the psychosocial factors that had been discussed. Even if they were relevant, he doubted if a general population survey like the ECA Program would yield the necessary information to demonstrate causation or modifiability. He dismissed any comparison between known risk factors for the major mental disorders and cigarette smoking as a risk factor for lung cancer, with the exception for heredity. Although the psychosocial work group reached better agreement on specific variables than did the biologically oriented group, Kety did not think their variables were really any more promising as risk factors.

Dr. Guze offered some support to Kety's viewpoint. He echoed Dr. Erlenmeyer-Kimling's call for the definition of "clusters" of risk factors that are mutually reinforcing and recalled Dr. Buchsbaum's statement that even MAO could not be recommended yet because we do not know what other variables must be measured at the same time to make it predictive.

The complexity of even apparently well-established risk factors like social class was emphasized. Dr. Gottesman reacted as a behavior geneticist to Dr. Weissman's inclusion of this variable. He pointed out that we need to ascertain not only a person's present social class but also the social class of his origin, and this involves separate specification of maternal and paternal social class. Dr. Bruce Dohrenwend seconded this view.

Dr. Buchsbaum was much more positive than Dr. Kety or Dr. Guze. He pointed out that the person best able to state the case for a particular measurement or risk factor is often reluctant to press the point in a gathering of scientists who will be much less enthusiastic. It was his opinion that some risk factors have indeed reached the stage where they need to be studied in a large, representative population. Without claiming expertise, he mentioned urinary MHPG, the continuous performance task, and unspecified familial drug responses.

HOW CAN RISK FACTORS BE ADDED TO ONGOING STATE-OF-THE-ART EPIDEMIOLOGIC RESEARCH?

Dr. Buchsbaum pointed out that epidemiologic studies in most branches of medicine are already sufficiently biological in orientation to accommodate new biological measures rather easily. Mental health epidemiology, in contrast, has traditionally been more sociological in nature, and a large change in orientation is needed to embrace biological risk factors.

Dr. Regier said that the next round of ECA studies, still very tentative, might be designed from the start to include selected risk factors or to allow additional variables of diverse types. Whether there ought to be another round, and when, will depend on the number and suitability of new questions to be asked and new tests to be done.

OTHER EPIDEMIOLOGIC SETTINGS FOR RISK FACTOR RESEARCH

Dr. Guze voiced the concern of many of the participants that so much discussion was being addressed to the ECA Program. He felt a need for further general discussion of risk factors and for attention to other opportunities to study risk factors for the major mental disorders.

Dr. Regier reaffirmed that the meeting had been called to ascertain the state of risk factor research in a broad context. Discussion had dwelt somewhat more on the ECA plans than was anticipated even by staff. The present ECA plan was relevant to this meeting mainly as an example of the setting which another round of studies might offer for risk factor research. This was an appropriate occasion to suggest new design features for epidemiologic studies of risk factors.

There are other large-scale health studies in progress or in planning stages to which mental health risk factor items may be added. Principally, these are represented by the National Health Examination Survey, conducted periodically by the National Center for Health Statistics and modified to meet new purposes each time. The next survey in the series will be a rather small one focused on Hispanics and incorporating an

abridged version of the DIS. Another later survey will be more like the recent National Health and Nutrition Examination Survey.

Dr. Kramer noted that the "natural experiment" (as discussed earlier by Dr. Gruenberg) provides an important potential context for risk factor studies. Such special situations may permit crucial tests of a single risk factor, as illustrated by the Copenhagen adoptee studies in schizophrenia, which tested heredity.

THE RELEVANCE OF EPIDEMIOLOGIC STUDIES TO ETIOLOGY AND PREVENTION

Dr. Kety's thesis that preventive intervention programs should, in our present state of ignorance, be based on knowledge of etiology evoked some dissent, especially from Dr. Gruenberg. That epidemiologic studies are a poor approach to understanding etiological pathways was more strongly contested, as was Kety's admonition that large epidemiologic projects, and targeted research in general, are competing with basic research into etiology of mental disorders. Dr. Klerman reminded the group that much of the targeted research is supported from funds earmarked by Congress. Four areas stand out in this regard: psychopharmacology, rape prevention or control, aging research and aging aspects of mental health, and research on minorities. At this point, as in his concluding remarks, Dr. Klerman emphasized the relatively protected position of investigator-initiated research and the small budget for epidemiology of mental disorders. The latter remains less than 10 percent of the total research portfolio across the three institutes of ADAMHA. Dr. Kramer said that the budget for epidemiologic research on the mental disorders has always been quite small in relation to the amount expended for such purposes in the National Cancer Institute and the National Heart Institute. Increases in the epidemiology budget of NIMH had done little more than keep up with inflation and had certainly not adjusted to the increasing cost of large-scale epidemiologic surveys.

Dr. Buchsbaum had been the first to say that our ignorance of etiology of mental disorders is almost total. In part this is because, ironically, when occasionally the etiology of a mental disorder is explained, the disorder is removed from the province of psychiatry. The great need for knowledge of causes simply means that etiological relevance should be, at this stage of our knowledge, an important criterion for study of a risk factor. There is good reason to think, for example, that MHPG excretion levels are relevant to etiology of mental disorders because MHPG is the major metabolite of norepinephrine in human brain tissue.

Dr. Kety affirmed the importance of epidemiology but said he and others in the basic sciences would like to see a greater readiness on the part of NIMH to support new ideas in fundamental research. This calls for new committees as new fields are opened. For example, there are clues connecting schizophrenia to virus research, but present NIMH study sections are not knowledgeable about virology.

THE EVOLUTION OF MENTAL HEALTH EPIDEMIOLOGIC RESEARCH

Dr. Gruenberg offered an explanation of the apparent decline in mental health epidemiologic studies in the 1960s, namely, that psychiatric epidemiology was largely

absorbed into other specialties. Now we need to bring these disciplines together again and let the epidemiologists benefit from the expertise of the other specialists.

Dr. Kramer suggested that psychiatric epidemiology in the 1960s was hampered by the disparagement of psychiatric diagnosis. Also, the CMHC movement shifted the focus of mental health epidemiology and raised unfulfillable expectations. Mental health programs suffered in schools of public health because interest in "promoting mental health" replaced the goal of preventing and controlling mental disorders. Public health approaches are appropriate, however, and require a lot more budgetary support than it seems possible to obtain now.

Dr. Gruenberg stressed the importance of targeted research in epidemiology. While insisting that investigator-initiated projects deserve continued strong support in the form of research grants, he felt that some large-scale studies like the ECA Program are quite necessary and need strong guidance at the Federal Government level. Long-term planning is particularly useful in order to encourage and develop career epidemiologists.

This does not necessarily mean, Dr. Gruenberg said, that mental health epidemiology should invest in such a long-term project as the Framingham study. That would be a difficult decision to make. Much the same result can be obtained in a 5-year, overlapping, longitudinal design in a population sample spanning a wide range of ages—a more realistic design in the present state of research technology.

ANOTHER MEETING?

Failure of this conference to produce firm recommendations for a program of research on risk factors led several to propose a second, similar meeting. Such a return engagement should be differently structured in order to focus precisely on the research context and to encourage specific proposals. If a major new project is to be considered, it would be helpful to invite someone from the Framingham study who could review first-hand the problems and the state of knowledge that gave the background and foundation for that project design.

CONCLUDING REMARKS

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Administrator, 1977-1980
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INTRODUCTION

Let us turn to two important program planning functions related to the issue of risk factors. One is the need for epidemiology data, and another is prevention programing.

The area of epidemiology has received more attention at this conference than the area of prevention. Given the public policy call to do more in the prevention area, it may be useful for this or some other group to discuss prevention at a similar forum in the near future. Concern over prevention was expressed in the Report of the President's Commission on Mental Health. Recently, Congress mandated that 7 percent of the drug abuse and alcohol budgets this year be set aside for prevention, with 10 percent to be set aside next year. This is a percentage of the funds allocated to treatment services and does not pertain to research budgets. The move illustrates the concern of Congress over the response of the Executive Branch to the needs for stronger prevention services in the fields of alcoholism and drug abuse. Considering our present knowledge, we have not always been sure how effectively we can invest more funds in prevention.

PREVENTION

With respect to mental health, the President's Commission called for the establishment in NIMH of a separate administrative unit on prevention. Moreover, $86 million was added to the research budget for prevention-oriented research. In the Mental Health Systems Act now before Congress, a proposed prevention Title would authorize NIMH to give grants to States and communities for prevention services.

This heightened attention to prevention should not be construed as reflecting inactivity on our part. On the contrary, some $35 to $50 million are already being invested in prevention in mental health fields. The issue is not whether we expend money on prevention but, rather, whether it is being used effectively and efficiently.

It appears that many who now call for an emphasis on prevention have in mind what we consider to be secondary prevention. That is, they would like to increase such activities as operation of hot-lines and the number of films devoted to encouraging people to enter treatment. Many Americans assume that a course in high school will

deter teenagers from smoking marijuana or becoming pregnant or driving automobiles while under the influence of alcohol.

It is the pressure from the health policy arena, coupled with the substantial funds already being expended on prevention, which summons our greatest wisdom and expertise. I hope that you may deliberate with us on the issue of more effective, rational means of prevention in these health areas, and I invite your consultation.

EPIDEMIOLOGY

In the area of epidemiology, the situation is far better, not only in mental health but also in alcoholism and drug abuse. Here again, it may prove beneficial to invite a group of authorities to examine the issues in mental health epidemiology and comparable problems related to alcoholism and drug abuse.

The papers presented here and the discussions which follow indicate that there is a growing interchange between the small band of psychiatric epidemiologists and the larger cohort of clinical investigators in psychopathology and biology, including genetics, pharmacology, and biochemistry. This interchange illustrates a profound intellectual change in the field. Dr. Myrna Weissman and I have described this development in an article which appeared in a collection of papers on epidemiology coordinated by Dr. Daniel X. Friedman for the Archives of General Psychiatry (35(6):705-712, June 1978).

The previous golden era of American psychiatric epidemiology occurred in the period immediately following World War II, when investigations, such as the New Haven, the Midtown, and the Nova Scotia studies were generated. It was a period heavily influenced by the social sciences and marked by emphasis on a unidimensional approach to mental illness whose measures were health, illness, and disability. There was little emphasis on diagnostic ascertainment of discrete disorders. Even in the recent "third wave" report of Dr. Leo Srole, there remains what appears to be a theoretical challenge to the relevancy of the concept of discrete disorders to the mental health field.

The period was characterized also by a concentration on psychosocial causes and the relevance of social class. Among the important studies of this genre were the Hollingshead-Redlich Work in New Haven which focused on psychosocial causes and the Nova Scotia studies of Alexander Leighton which explored the role of social stress. There was a corresponding deemphasis on genetic and biological causes. Despite what we may now consider to be theoretical biases in that generation of studies, there were, nonetheless, some significant achievements. One was refinement of the technique of sampling and of the household-survey method derived from the social sciences. These methods, applied with great rigor, were developed for estimates of social class and life events which have enlarged the domain of independent variables.

In retrospect, it seems that this golden era of psychiatric epidemiology entered into relative decline in the late 1960s and 1970s. Meanwhile, during the two most recent decades, biology underwent tremendous expansion—particularly genetics, neurochemistry, neuropharmacology, and clinical psychology. In psychopathology there is an attempt to improve the reliability and validity of diagnostic criteria. Several of our colleagues here today pioneered in operationalized criteria for inclusion and exclusion, which later culminated in the RDC and the DSM-III, led by Robert Spitzer. Also participating in this conference are colleagues who were involved in developing new

methods for statistical estimates of reliability. These efforts have been incorporated into the current wave of epidemiologic studies now underway in New Haven and St. Louis and scheduled to begin soon in Baltimore. The new studies are designed to include measures of discrete individual disorders, with reliable and even partially validated criteria for inclusion and exclusion.

It is not clear from these discussions whether new advances in biology are to be included. It is not so much ideological resistance, as may have been the case in the 1950s and 1960s, but rather, the lack of certainty over including biological advances reflects some concern that biological measures—whether electrophysiological or biochemical—have not developed to the stage of reliability and validity required for application in either large-scale pedigree studies or community studies, whether cross-sectional or longitudinal.

Based on these discussions, it would appear that, while great advances have been made in genetics, neurochemistry, and neuropharmacology, little agreement exists on even half a dozen biological measures. This may signify that more may be needed or that more meetings such as this should further opportunities for interchange between epidemiologists and social and biological psychiatrists and clinical investigators.

ROLE OF ADAMHA AND INSTITUTE STAFF

A final comment, in connection with our public health responsibility, concerns the role of the government in stimulating research in areas of public health needs. Since World War II, with initiation of the Public Health Service program in NIH, and later the functioning of the Institutes of ADAMHA independently of NIH, the preferred mechanism for the Federal support of research has been through the investigator-initiated proposal. These proposals are subjected to peer review by study sections and review committees. This is the predominant mode for the funding of more than 60 percent of medical research today. This mechanism, as attested to by both the Woodbridge and Murphy committees, has proven successful, more so for the laboratory and biomedical sciences than for the behavioral and psychosocial sciences. Nonetheless, Congress is extremely protective of this mechanism.

At the same time, a number of areas with high public health needs have not advanced as rapidly through investigator-initiated research. Examples are toxicology and clinical nutrition. Although there is a decided public health need for evaluation of toxins, particularly carcinogens and industrial toxins, for inexplicable reasons these areas have attracted few researchers. This is a real cause for concern. Similarly in our field, the judgment is that the spontaneous investigator-initiated grant has not kept pace with the public health need.

It is our responsibility, therefore, to supplement the spontaneous, investigator-initiated proposal by implementing various administrative devices to support and encourage a particular field of endeavor in which a gap exists between public health need and the discerned rate of scientific progress. Numerous mechanisms are employed to achieve this end. One is the earmarking of money, either by Congress or ADAMHA. Another is the use of staff-initiated collaborative designs. The field of epidemiology currently affords an example of the latter. Some may think the amount of funds devoted to these collaborative arrangements is too little; others hold the view that they are being undertaken at the expense of spontaneous proposals. Nonetheless, the public health need

for certain data is clear, and, on this basis, we must stimulate and encourage various fields of inquiry.

Therapeutics research is another area of current concern. The evaluation of psychotherapy is important, since the gap between public health need and available knowledge is even greater than in epidemiology.

I recognize that there is some apprehension in the field. The best way to deal with that apprehension is to make the issue a topic of open discussion in an interchange between key persons in the Federal government who are responsible for such decisions and men and women in the scientific community. Discussions such as those we have engaged in here can address the matter. As an amateur scientist in epidemiology and as an amateur politician administrator, I have found this a learning experience. It may be helpful for future meetings to start off with a brief, 2-hour survey of risk factors and the distinction between attributable risk and relative risk in public health. One should not presume a greater diffusion of epidemiologic concepts among clinicians, geneticists, and psychopathologists than is, perhaps, the case. Again, it may be useful to convene another meeting of this size to discuss the future of the Epidemiologic Catchment Area Program and to give some consideration to the wisdom of a second generation of studies based on a longitudinal prospective design, whether short-term or for a longer period.

EDITORS' SUMMARY

The purpose of this conference was to sample current expert opinion on the state of knowledge of biological and psychosocial risk factors for the major mental disorders. The impetus derived from at least two sources: (1) the current emphasis on prevention, which requires understanding of risk factors for intervention, and (2) the ongoing large-scale epidemiologic studies on incidence and prevalence of discrete psychiatric disorders, which provide an opportunity to study those risk factors identified as potentially important.

The participants were not asked to explore questions of etiology, and they did not. They also did not recommend intervention programs on a service basis that could prevent mental disorders in the near future. Some participants did suggest prevention research on early or late interventions, and some offered guidelines for other types of risk factor research. The working groups considered what specific risk factors might deserve early inclusion in epidemiologic studies and recommended criteria for setting priorities. In this chapter, we attempt to bring together the essentials of both the advance working papers and the discussions that took place during the conference.

HISTORY AND METHODS OF RISK FACTOR RESEARCH

A variable is termed a risk factor for a specific disease when it is found to be associated with increased risk of the disease. Risk factors are particularly useful when they elucidate etiology and suggest a method of prevention, but the term does not necessarily imply a causal relation. Causation by the factor in question may be very difficult to establish, even if it exists, and risk factors unrelated to causes may be useful in directing attention to persons who are most likely to suffer future onset.

An established risk factor is likely to suggest etiological hypotheses, and, conversely, knowledge of etiology may lead to discovery of risk factors that identify susceptible individuals. A risk factor may be either an environmental circumstance, such as early loss of a parent, or an individual trait, such as a rare blood antigen. Many marker variables suggested as risk factors on the basis of clinical studies later prove to be "state markers," as Dr. Prange called them, results of the disease or its treatment. These may be important for treatment or diagnosis but not for predicting the disease.

History

Dr. Gruenberg traced the history of risk factor research from the simple concept of a risky venture, such as a sea voyage, through the development of insurance systems to public health applications in controlling or preventing disease. Life insurance methods focused originally on the probability of dying. Preventive medicine is more concerned with the probability of becoming ill, in modifying this probability, and in assessing or altering prognosis and the course of disease. Risk factors are the indices necessary to these ends.

Quantitative Risk

Risk factors for incidence of a disorder relate to likelihood of onset of the disorder; risk factors for prevalence relate to onset and also to length of survival after onset or to duration of symptoms. For the most part, these proceedings focus on risk of onset. Available measures of onset, however, are influenced by prevalence; thus, first hospital admissions are often taken as a measure of incidence, admittedly biased by help-seeking behavior and socio-demographic variables, but they also reflect duration and progression of illness.

Risk of onset usually varies with age, which must therefore be controlled in any comparison. The effect of other possible risk factors can be expressed as a **contingency risk** or, better, as a **relative risk.** The latter quantity, to be directly measured, requires data on incidence of the disorder obtained in prospective studies, but it can be estimated indirectly in retrospective studies by the "odds ratio."

Still more informative is **attributable risk,** the amount of disease attributable to a risk factor. Dr. Gruenberg provided a formula for estimating attributable risk from relative risk and the proportion of the population exposed. The ideal measurement of attributable risk, however, would require demonstration of a causal relation, usually by means of a preventive trial.

Risk Factor Research Designs

The most direct approach to risk factors is the prospective study, which collects disease incidence data in a community or cohort subdivided by presence or absence of the trait or experience in question. When developmental observations are needed, a time-saving modification is the overlapping prospective study, which follows overlapping age cohorts for several years. Still more time can be saved in the nonconcurrent prospective design, which ascertains persons with relevant exposure history, such as famine, and examines the prevalence among them of the disease in question. Much more economical is the case-control retrospective design, heavily used in epidemiology. This design starts with clinical cases and suitable controls and elicits history of exposure or nonexposure to the suspected risk factor. Both this and the nonconcurrent prospective study may fail to establish a risk from lack of a suitable control group.

The preventive trial is, of course, valuable in establishing a risk factor as an etiologic agent and is ultimately necessary to test a potential means of controlling the disease. Despite limited applicability of preventive trials in mental disorders, Dr. Gruenberg cited recent use of the method in prevention of the Chronic Social Breakdown

syndrome. He pointed to some present opportunities for preventive intervention: improving maternal nutrition long before conception occurs, widow-to-widow counseling, and reeducation of young mothers with low self-esteem.

DISTINGUISHING DEPENDENT AND INDEPENDENT VARIABLES

In prospective epidemiologic research, the risk factor is taken as the starting or independent variable, and onset or aggravation of the disorder is the outcome or dependent variable. Difficulties arise in the definition of the outcome and in assuring that the risk factor is indeed an independent predictor rather than an early manifestation of the disorder.

Definition of the Disorders

Fortunately, this meeting did not lose much time debating definitions of diagnostic entities, even though the focus was on risk factors for **specific** mental disorders. The diagnostic system embodied in DSM-III was accepted as the standard, where necessary. One obvious difficulty is that nearly all research to date has been based on older systems, and equivalence between old and new entities is often obscure. Moreover, past research has too often been dominated by diagnostic practices that expressed social biases. Dr. Guze commented, in connection with the personality disorders, that, if researchers will observe the diagnostic criteria associated with DSM-III, useful new findings ought to result within the next five years.

The adoption studies cited by Kety and Kinney reveal no genetic relation between "acute schizophrenia" and the chronic forms but link the latter with a spectrum of lesser disorders implied by Blueler's term, "latent schizophrenia." The genetic heterogeneity revealed by adopted studies does not entirely conform to the DSM-III subtypes.

Heterogeneity in the affective disorders is compounded by heterogeneous methods of measurement. The research cited by Hirschfeld and Cross, Eaton, and the Dohrenwends relates variables to "depressive symptomatology," to the depressive syndrome, and only rarely to unipolar versus bipolar depression. Community studies usually deal with depressive symptoms or overall impairment, while clinical studies deal with the syndromes and the subtypes of depression. Each category can be further subdivided.

Anxiety disorders share common ground with depression, on the one hand, with respect to both symptomatology and associated variables. On the other hand, the anxiety disorders of DSM-III include only a few of the older "neuroses," while the phobias, which are included, are often not accompanied by manifest anxiety. Nevertheless, it seems from Dr. Marks' review that most of the research on etiology and treatment of neurosis can be referred to the newly created category of anxiety disorders.

The personality disorders are the most difficult to describe operationally or to differentiate from one another. DSM-III does not classify them as alternatives to the major mental disorders but places them on a different "axis," permitting cross-classification with the other three major disorders. Two of the best-defined personality disorders are, naturally, also those most studied: antisocial personality and histrionic (e.g., hysterical) personality. Even these have been poorly defined in most of the available research,

so that Martin and Guze were not able to point to strong research evidence for risk factors specific to either disorder.

Proximate and Ultimate Risk Factors

To be useful in short-term research projects or intervention trials, a risk factor must be detectable within an interval of, at most, five years preceding breakdown. If the risk factor is a cause of disorder, it might have exerted its action much earlier, perhaps even before birth in the case of a genetic trait. Still, if it is persistent or even preserved in a medical history, it can serve as a proximate risk factor for identifying persons at greatest risk. A blood antigen that served as a genetic marker of susceptibility to schizophrenia would be a very useful risk factor, whether the gene acted before birth or after puberty.

An ultimate or early cause is unlikely to be modifiable in the individual but presents an opportunity for long-term prevention by public health measures. Kety and Kinney stressed the evidence for prenatal and natal causation of some cases of schizophrenia, with a finger pointing at poverty and attendant environmental conditions of nutrition, exposure to infectious agents, and related poor obstetric and other health care. The importance of such risk factors in elucidating the etiology of schizophrenia and eventually in preventing it is obvious. They can contribute little, however, to short-term research or to late prevention.

The prospective high-risk studies of schizophrenia described by Dr. Garmezy assume, in most instances, that genetic or prenatal factors are of etiological importance. This is not necessarily incompatible with the concept of multiple causes. Dr. Garmezy emphasized that early deviance detectable in the offspring of schizophrenics cannot yet be regarded as strongly indicative of later psychosis. It therefore seems worthwhile to look for proximate causes and proximate risk factors, even when an ultimate predisposing cause is strongly suspected.

Causes versus Effect

Determining the time of the onset of disorder is often crucial in identifying causes and planning intervention strategies. Life-events research in depression has been plagued by the difficulty of separating genuine external stress from events colored as stressful by an incipiently depressed subject, or even precipitated by his passive or negative behavior. Dr. Bunney described a frequently observed sequence in which life events appear in retrospect to trigger a spiral of deepening depression and further stressful events. Were the later events sequellae of the earlier ones, or were they independent, their accumulation finally overcoming the patient's tolerance and bringing him/her to medical attention? To resolve this issue, prospective studies are needed which define events both objectively and in context and which specify the outcome in terms of well-defined diagnostic categories.

RISK FACTORS OF IMMEDIATE INTEREST

During the two days of the conference, particularly in the working groups, a large number of variables were mentioned as potential risk factors for mental disorders. Many

of these are discussed, or at least mentioned, in our summaries, including possibly all that have high potential on the basis of present evidence. We discuss below the attributes of risk factors and the criteria which emerged as most useful in identifying risk factors worthy of strong research support. We then consider separately (1) those that can be considered for a survey of adults in the next 2 or 3 years and (2) those that require and clearly deserve to be further studied in selected populations.

Attributes of Risk Factors

Certain general properties of risk factors need to be emphasized before we present specific criteria for selecting them. Most important is the distinction, already mentioned, between state markers and trait markers. State markers are illustrated by screening criteria for the presence of disease, but they might also be signs of a reversible, preclinical state which would be useful in prevention. Generally, however, a good risk factor is one that is stable over long periods of time so that its presence can predict disease in a reliable fashion. In other words, a risk factor is a trait marker associated with the subsequent occurrence of disease.

Methodologically, risk factors can be evaluated in the same way that screening tests are evaluated, the common criterion being the occurrence of the disease state. Sensitivity in a screening test refers to "the probability of a positive test **given** that the disease exists" (Bahn, A.K. Basic Medical Statistics. New York: Grune & Stratton, 1972, p. 185). Sensitivity of a risk factor is the proportion of individuals destined to acquire a disorder (barring intervention) who can be identified in advance by the risk factor. If a disorder like schizophrenia is heterogeneous in etiology, risk factors related to etiology will appear not to be sensitive to the disorder as a whole but may be highly sensitive for the respective etiologic types of schizophrenia.

Specificity of a screening test is "the probability of a negative test given that disease does not exist" (Bahn, op. cit.). Specificity of a risk factor is the proportion of nonsusceptible persons who can be identified as nonsusceptible on the basis of the risk factor. Data that yield estimates of both relative and attributable risk generally permit statements of sensitivity and specificity. The disease or disorder of interest must, of course, be precisely defined. Specificity for a narrowly defined disease like phenylketonuria is often more useful than specificity for a group of disorders like mental retardation, at least in developing effective interventions. Sensitivity and specificity can be enhanced by combining risk factors.

If a risk factor is found to be highly specific or highly sensitive for a disease, it should be associated with a sufficient or a necessary cause of the disease, respectively. It does not appear that any such risk factors can yet be identified for the major mental disorders.

In addition to state and trait markers, risk factors include exogenous causes, such as economic depression or natural catastrophe. These are usually viewed as precipitants of mental disorder, but at a longer interval before breakdown they could conceivably cause vulnerability. Such events relate to populations more than to individuals but lend themselves to research in etiology and prevention of mental disorders. Recent life events are similarly assumed to play a precipitating role, while early family events may cause (or reduce) vulnerability. If early events cause vulnerability and appear in a person's history, they may be treated as trait markers.

Criteria for Selecting Risk Factors of High Potential

Different sets of criteria were developed by the two working groups for rating the potential value of a risk factor. Both sets were coherent and more or less complete, but they differed considerably in structure and detail. Here we attempt to distill the best of both.

1. Readiness for application. This criterion separates risk factors into those which can be considered for immediate inclusion in plans for a survey and those that require additional study on clinical and control populations. Some tentative risk factors are suitable for immediate consideration if good measuring instruments are available and only large-scale testing can add new information.

   Ranking of other criteria is rather arbitrary. It may depend on purposes for which risk factors are to be used and on the category of a risk factor under criterion (1). The next three, like the first, are essentially qualitative.

2. Etiological relevance. Variables that may be postulated to cause a disorder directly are obviously the most valuable. Other alleged risk factors which suggest or test etiological hypotheses are also important to study.

3. Modifiability: This is clearly important for ultimate applications to prevention.

4. Familial occurrence or transmission of the trait. This will often imply that the risk factor is genetic and a possible marker for genetic susceptibility. Failure of a risk factor to meet this criterion should not be a strong reason for neglecting it.

5. Sensitivity and specificity. As explained above, these measure the usefulness of a risk factor in predicting a disorder. High specificity is desirable not only in the sense of excluding false positive results but also in the sense of predicting a narrow diagnostic entity within a larger category for purposes of etiological research and of intervention.

6. Weight of empirical evidence. Association with mental disorder should be already established by appropriate research, but a tentative risk factor of theoretical importance might be included in a large study in order to validate the association.

7. Numerical importance. Magnitude of exposure of the population may be as important as magnitude of the attributable risk.

8. Stability. The term, trait, implies some stability, but this is relative. Even a genetic trait may be expressed only within a limited age span.

9. Measurability. A reliable instrument is needed which can be readily used in the field or, if the research design permits, on subjects brought into a clinical setting in rather large numbers.

10. Prospect of scientific payoff. Even when a variable is not thought to be etiologically relevant to the associated disorder, it may have clear ancillary usefulness in answering important biomedical questions.

Risk Factors to be Considered in Current Survey Planning

Some of the following variables are listed because they are easy to ascertain, rather than because they are strongly associated with mental disorder. The order of presentation is arbitrary.

Risk Factor	Principal Specificity
Sex	Major and minor depression, personality disorders
Age	Schizophrenia
Marital status	Schizophrenia, minor depression
Social class	Schizophrenia, antisocial personality
Employment status	Schizophrenia, minor depression
Family history of mental disorder	All mental disorders
History of perinatal complications	Schizophrenia
Blood and tissue samples to be preserved for future tests for antibodies or genetic markers	All mental disorders
Measures of attentional deficit, e.g., Continuous Performance Test	Schizophrenia, antisocial personality
Recent life events	Major and minor depression
Early family events	Major and minor depression

Tentative Risk Factors that Merit High Exploratory Research Priority

Most of the above variables, even though ready for use in epidemiologic studies, also warrant continued small-sample research, either to refine the measurements or to explore their etiological significance. Many other promising risk factors require better confirmation or better definition, or their interactions need to be explored. Life-events research, for example, still faces many difficult problems. Some variables, including the principal somatic or biological markers at the head of the following list, are difficult to ascertain or measure in large populations. Others require further studies on clinical samples. Nearly all can be fruitfully investigated in high-risk subjects such as relatives of cases or in combinations with other risk factors. Some variables may be better viewed as moderators of risk rather than as risk factors per se. Clearly, theoretical models of etiology are of value in the selection of meaningful clusters of risk factors.

This list is only a sample of the tentative risk factors suggested at the conference.

Platelet monoamine oxidase

Average evoked potential (electroencephalogram)

Urinary 3-methoxy,4-hydroxy,phenylglycol (MHPG)

Blunting of Thyroid Stimulating Hormone (TSH) response to Thyroid Releasing Hormone (TRH)

Plasma cortisol dexamethasone suppression test

Social and coping skills or current adaptive functioning

Intelligence

Health history and current health status

Expressed emotionality of the family

Type of residential area

Social class of each parent

Religion and ethnic identification

Size and composition of family of orientation

Psychological or medical problems in subject's children

PROSPECTS OF IMPLEMENTATION

Opportunities

The current round of Epidemiologic Catchment Area projects supported by the NIMH Division of Biometry and Epidemiology is too far advanced to permit any substantial addition of risk factor studies. There is, however, possibility of a second round of large-scale population studies—either investigator- or government-initiated—following completion of the first round, which could give a prominent role to risk factors. A more assured opportunity, but giving only secondary attention to mental disorders, is offered by the periodic surveys conducted by the National Center for Health Statistics. Such surveys and cross-sectional studies can establish associations and generate hypotheses, provided that diagnoses are objective and standardized. This proviso has been an obstacle, particularly to risk factor research in the personality disorders, and it remains to be seen how well that is overcome by the advances represented in DSM-III.

Other possibilities for large-scale risk factor studies include natural experiments provided either by catastrophes such as earthquakes or by social conditions such as unemployment. These designs merge with smaller-scale projects such as recent-life-events research or innovative, interdisciplinary investigations of small samples. Both large and small studies of good design are likely to be supported or sponsored by NIMH in line with high priority placed on identification of risk factors. The emphasis in this conference on epidemiologic approaches reflects the interest of the NIMH Division of Biometry and Epidemiology. Cross-sectional and follow-up studies of patient populations are no less important and should be strengthened and refined in lock step with epidemiologic research; they are represented in the Intramural and Extramural Research Programs, cosponsors of the conference with DBE.

Gruenberg's enthusiasm for preventive trials was shared by many participants and undoubtedly prevails in the mental health professional community at large. The three divisions of NIMH that sponsored the meeting share equally the ultimate objective of prospective studies of high-risk groups which focus on risk factors and prevention. Steps in the direction of benign, positive intervention were proposed at several points (Gruenberg, Garmezy, Kety), and somewhat more intrusive strategies were suggested by Marks (see below) and Gershon. No consensus was reached on these issues, but lively discussion was evoked by Gershon's proposal to locate relatives of patients for early detection of illness. Ironically, when Garmezy and, less explicitly, Kety advocated good prenatal and postnatal care for women with a history of severe mental disorder, no voice was heard suggesting support for family planning assistance. Genetic counseling was, however, mentioned in Dr. Gershon's paper and discussion.

Other Research Needs

The visible opportunities for risk factor research are principally surveys and very short-term studies, which have limited potential for revealing temporal relations. Much can still be done with retrospective studies of various designs, such as those suggested by Kety and Kinney, but full confirmation of risks requires genuine longitudinal research or even intervention experiments.

To date, only the studies of children at risk for schizophrenia have begun to provide an appropriate time frame for confirmation of risks. These have tended to disconfirm suspected risk factors and to yield new ones such as attentional deficit. Shorter-term, overlapping prospective studies might have achieved the same ends, if sufficient subjects could have been found, by calling attention to risk factors useful in adolescence and tracing these variables back to earlier ages.

Other specific longitudinal designs were proposed in three of the formal papers. Marks suggested several types of intervention, beginning at age 10, to test at least the preventability of specific anxieties and phobias that may emerge 15 years later. Eaton suggested both shorter-term and longer-term studies that do not require intervention: a 1-year span focused on changes of employment or marital status, and a 20-year study focused on primary social networks, starting at age 15. The Dohrenwends proposed a short prospective study of cases and controls which would start with multiple baseline measures, including thorough clinical evaluation. This would be followed with careful monitoring of life events every few months and a repetition of diagnostic and some other measures after a year or more.

Support

The largest surveys require organization and funding at a national level, but this may be achieved either by a single massive study in the pattern of the National Health Examination Survey or by a collaboration among institutions with partially standardized protocols, like the present ECA program. Choice among these alternatives will depend both upon legislative initiatives, particularly the NIMH budget for epidemiology, and upon interest and initiative on the part of qualified investigators.

Some concern was expressed at the conference, and is recorded in this volume, about the danger of competition between government-directed epidemiologic research on risk factors and more basic, investigator-initiated research on etiology of mental disorders. Our view of the issue is that basic epidemiologic research is an essential complement to laboratory and clinical research, providing an important context of prevalence and incidence data for the disorder under study. It also enables investigators to verify or correct conclusions based on samples that may have been atypical or biased. The decision as to which research should be government-directed and which should be investigator-initiated will depend on the degree to which public health research needs are addressed without government intervention. There has not been evidence to date of direct competition between epidemiology and other basic research; a relatively small amount of funds (about $2 million per year) has been devoted to government-initiated epidemiologic research.

Planning

Many participants at this conference were reluctant to recommend particular risk factors for use in epidemiologic surveys. Clearly, much additional planning will be needed, involving not only NIMH staff but outside experts including some of those who attended this conference. Before a serious planning session is organized, it will be necessary to set objectives, to define the research setting, and to ascertain the amount of Federal support that can be marshalled.

Pending such a conference and, no less, as further progress is made in the study of risk factors, it would be highly desirable to maintain good communication among scientists doing risk factor research. Dr. Buchsbaum is making an effort to publish results of risk factor research with minimal delays in the new journal, Psychiatry Research. A systematic schedule of reviews in the field would be desirable as well as regular conferences, or sessions within larger meetings, about progress in various groups of risk factors. Finally, individual scientists are encouraged to communicate their findings not only in formal publications and meetings but also in frequent personal contacts.

Design

The biggest problem in design of risk factor research is probably the choice of appropriate clusters or combinations of variables. This choice can be aided by theoretical models of causation that integrate available, relevant knowledge. The value of combining the right variables is emphasized in several papers in this volume and has been dramatically illustrated by research findings on monoamine oxidase and evoked potentials. Only certain combinations of those measures seem to be closely associated with specific disorders; either measure alone is much less useful. Cross-disciplinary collaboration may also be essential. It will be important for the planning to involve biologically oriented scientists in close collaboration with epidemiologists, augmented as needed by sociological and psychological scientists.

Multiple facets are needed in the approach not only to risk variables but also to the outcome variables, to ensure valid and consistent diagnoses where previous research has accepted gross categories such as "depression." Decisions must be reached on such important issues as size of population, age range of subjects, stratification or selection of the sample to obtain higher risk subjects, and whether, after screening, to bring some subjects into a clinical setting for more demanding tests. All these issues are considered in this volume.

GLOSSARY OF ACRONYMS AND SIMILAR ABBREVIATIONS

BP	bipolar (affective disorder)
CD	communication deviance
CES-D	Depression Scale of the Center for Epidemiologic Studies
CMHC	Community Mental Health Center
CNS	central nervous system
COMT	catechol-O-methyl-transferase
CPK	creatine phosphokinase
CPT	Continuous Performance Task
CRB	Clinical Research Branch (of NIMH)
CSBS	chronic social breakdown syndrome
CSF	cerebrospinal fluid
CT	computerized tomography (X-ray)
DBH	dopamine- -hydroxylase
DIS	Diagnostic Interview Schedule
DNA	deoxyriboncueic acid
DSM	Diagnostic and Statistical Manual of the American Psychiatric Association (editions II and III)
DST	dexamethasone suppression test
DZ	dizygotic (two-egg, twins)
ECA	Epidemiologic Catchment Area
EE	Expressed Emotionality
EEG	electroencephologram
EP	evoked potential (on EEG)
GH	growth hormone
GSR	galvanic skin (electrodermal) response
HLA	human leucocyte antigen
HPA	hypothalamic-pituitary-adrenocortical
ICD	International Classification of Diseases
IQ	intelligence quotient
Li	lithium
MAO	monamine oxidose
MHPG	3-methoxy-4-hydroxyphenylglycol
MMPI	Minnesota Multiphasic Personality Inventory
MZ	monozygotic (one-egg, twins)
N	number--sample size
NIMH	National Institute of Mental Health
OC	obstetrical complication
PSE	Present State Examination
RBC	red blood cell
RDC	Research Diagnostic Criteria
REM	rapid eye movement (sleep)
SADS	Schedule for Affective Disorders and Schizophrenia
SCR	skin-conductance (electrodermal) response

SDAT	senile dementia, Alzheimer's type
S-R	stimulus-response
SES	socioenvironmental status
Ss	subjects
TAT	Thematic Aperception Test
TRH	thyrotrophic releasing hormone
TSH	thyroid stimulating (thyrotrophic) hormone
UCLA	University of California at Los Angeles
UP	unipolar (affective disorder, depression)
WHO	World Health Organization
Xg	a sex-linked blood antigen
XXY	an abnormal complement of sex chromosomes (Klinefelter's)
XYY	an abnormal complement of sex chromosomes
WAIS	Wechsler Adult Intelligence Scale

INDEX

Admission rates, 119,125-6
Adoptive studies, 43-8,97,99,145,187
Affective disorders, 55-64,69-76,146-155
  and anxiety, 66-7,88
  biological markers, 166-8
  demographic variables, 112-115,199
  diagnostic problems, 81,195
  in parents, 33,39
  life events, 132-5,196
Affective style, 34
Age (see Childhood topics), 10
  changes, 73,83,87
  depression, 56-7,112-3
  schizophrenia, 112,121
Aging research, 187
Alcoholism,
  and depression, 74,75,150,168-170
  family history, 97,146
  prevention, 189
Antisocial personality, 32,96-9,112-5,134,146, 199
Anxiety, 81,98
Anxiety disorders (see Neuroses), 81-92,146,195
Arousal, cortical, 98,101,167-170
Attention, 28,31,38,164-5,169,179,199

Bereavment (see Parental loss), 55,70,75,90, 134
Biological clocks, 75,87,91
Birth season, 46-7
Birth weight, 30
Brain trauma (see Obstetrical complications), 46-7

Case-control studies, 44-6,59,132-3,138,194
  design, 11-14
Casefinding, 120-1,153,155,161,179
Catchment areas, 5,153,175
Cause-effect relations (see Etiology), 111,129, 170,182
  demographic variables, 113-5,128
  life events, 58,107,133,138,142-3,196
Childhood disorders (see Age), 87-90,99,182,142
Childhood experience (see Mothering, Bereavement), 88,182,183
  home environment, 28,50,61-2,86
  personality disorders, 99,101,104
Children, research on, 38-9,182
Cholera, 90,128,179
Chronic Social Breakdown syndrome, 15-16,194
Cognitive functions, 31,118,143
Collaborative Program on Depression, 56-7
Colorblindness, 152
Communication deviance, 34
Communication, scientific, 179,203
Community integration, 116-120
Community mental health centers, 5,27,155,188
Community studies (see Surveys, Prevalence),
  depression, 56-8,67,195
  life events, 132-3
  methods, 5-6,153,175,190-1
  variables, 38,119
COMT, 148
Confidant, 60,88
Continuous Performance Task, 28,164-5,186
Control, locus of. See Helpessness, Learning
Coping skill, 17,90,118,134-5,182-3
Creatine phosphokinase, 151
Criminality. See Antisocial personality
Crowding, population density, 48,116-8
Culture (see Ethnic groups), 39,118,128,147

DBH, 148,169
Deinstitutionalization, 16,27,118,176
Dementia, 10,17,42
Demographic variables, 55-8,94,111-122,183,199
Depression. See Affective disorders
Dexamethasone, 74-5,200
Diagnosis, 41-2,66-7,103,126,161,190
  as outcome, 25,203
  role in research, 69,104,163
  versus symptoms, 5-6,188
DIS, 6,187
DNA technology, 148
Drug abuse, 149,155,189
DSM-III (see Research Diagnostic Criteria),
  impact on old data, 38,100,195
  validity issues, 81-2,96,102,103,201

Ecological variables, 116-9
Electrodermal response, 28,31-3,86,164
Electroencephalography, 76,86,97-8,167-9
Employment, 112,114-5,121,199
Environmental causes, 43-50,54,142
Epidemiologic Catchment Area,
  applications, 14,176,121-2
  development, 5-6,201
  limitations, 179-180,183,185,186

Epidemiology (see Research support),
careers, 180,188
definition, 8-9,111,145
history, 197-8,190
Ethnic group, 57,99,112-3,126-7,183,200
Etiology (see Cause-effect),
hypotheses, 30,116-120,136-7,200
relevance of risk factors, 76,128,179-180, 185,187,196-8
Evoked potentials. See EEG
Evolution, 83-5,91
Expressed emotionality, 34,79,200
Eye movements, 165

Familial incidence (see Pedigree studies),
high-risk families, 79,166
statistics, 145-7
interpretation, 43,50-1,54,85-6,152-3
Family structure, 32,119,135,184
Family studies, 27,33-4,50-1,161
Famine, 13
Fetal damage, 13,47-8
Field studies. See Surveys
Fluoridation, 15
Foster placement (see Adoptive studies), 30, 184

Galvanic skin response. See Electro-dermal response
Genetic counseling, 153,162,179,201
Genetic factors,
associated traits, 32,42,49,74,117,198
evidence for, 43,48,57,83-6,96-7,145-155
Genetic markers,
chromosomal, 152,199
physiological, 148-9,198,199
value, 44,161,176,196
Genetic models, 43-4,54,97,147,152-3,175
Grief, morbid, 90

Health, general, 60,184
Heart disease, 7,87,90,188
Helplessness-hopelessness (see Self-esteem), 118,134,143
Heterogeneity, 42,43,50,53,63,71,76
Histrionic personality, 100-1
Hormones, 73-7,86-7,200
Human leucocyte antigens, 152
High-risk research, 23-34,50-1,120,163-170, 179,200
Hyperactivity (see Attention), 99

Incidence, 10,14,125-7,194
Influenza, 49
Insurance, 9,10
Intelligence, 28,182,184
Interdisciplinary collaboration, 8-9,183,186-188,190,203
Intervening variables, 125,116-118
Intervention trials (see Prevention), 6-7,15, 129
design, 38-9,120-2,187,196
recommended, 17,89-90
value, 90,128,179,194,201

Learning, 98,134
Life events (see Childhood experience),
findings, 58-61,63,131-5,142
research design, 122,138,183-4
theoretical role, 70,87,136-7,196-7
Life table, 10
Linkage, genetic (see Genetic markers), 148-9, 152
Lithium, 151-167

Marital status, 57-8,112,115-6,122
findings, 57-8,112,115-6
interpretation, 60,128,122
Mauritius research program, 38-9,164
Measurement, 180
Medical care, 48,118
MHPG, 72,186,187
Midtown Manhattan study, 5,190
Modifiability, 9,111,122,175,182,183
Monoamine oxidase, 150-1,165-170
Mothering (see Childhood experience), 17,26-27,30
Multiple factors (see Study design),
causes, 60,64,143,203
test clusters, 39,166-170,181,185,197

Natal care (see Obstetric complications), 30, 118
Natural experiment, 13,187,201
Neurological deviance, 30
Neuroses (see Anxiety disorders), 81-92,100, 133,136,195
Neurotransmitters, 72,86,150
Nutrition, 13,16-17,47,49

Obstetrical complications, 13,26,30,44-7,199
Odds ratio, See Relative risk

Parental loss (see Bereavement), 62,88,131, 134,183
Pedigree studies, 70,145-155,175-6
Pellagra, 15,50
Peptides. See Hormones
Personal disposition (diathesis), 131,134-5
Personal resources, 60
Personality disorders (see Antisocial personality, 88,95-104,195-6,199,201
Personality traits, 31,61,86-8,95,165
Pharmacological responses, 72-6,88,148-9,186
Physiological responses (see Electro-dermal response), 70-1,86
Postpartum mental disorder, 30,56

Poverty (see Resources), 29,39,48,50,128-9
Preclinical status (see Risk factors), 27,87, 94,197
Prediction of disorder, 42,59,60,180,194,197
Prenatal care, 16-7,50
President's Commission on Mental Health, 4,189
Prevalence, 14,113-5,126-7,147,185,194
Prevention (see Intervention trials), 129
  advocacy, 4,189
  opportunities, 39,50,152-5,194-5,201
  prerequisites, 50,87,125,175,196-8
Prospective studies (see Childhood experience), 23-34,39,59,87,94,114-5,119
Psychodynamics, 98-9,101
Public health, 9,188,191,196

Race. See Ethnic group
Relative risk, 12,79,120
Religion. See Ethnic group
Research Diagnostic Criteria, 6,34,55,64,190
Research needs (see Prospective studies), Intervention trials), 69,81,89,121-2,155, 182-3,191-2,203
  depression, 63-4,176
  life events, 138-9,196
  risk factors, 170,180,200
  schizophrenia, 33-4,50-1
Research strategy, high risk, 23-34,163-170
Research strategy, national, 4,51,128-9,187-188,191
Research support,
  deficiencies, 148,187
  magnitude, 3,187,189
  priorities, 176,180,191-2,201,202
Residence, urban/rural, 48,112,115,183
Resources (see Personal resources), 117-8,135
Risk factors,
  anxiety disorders, 86-88
  criteria for use, 79,179-181,183,187,198-9
  definition, 69-70,111,193,197
  depression, 56-61,66,75-6,151
  personality disorders, 96-101
  schizophrenia, 26-7,29-31,43-9,151
Risk measures,
  estimation, 10-14,182
  history, 9,194
  types, 9-11,14,43,125,145,194

SADS, 6,165
Sampling, 103,120,175-6,183,188,190
Schizoaffective disorder, 75,152
Schizophrenia, 23-34,41-51,132-3,146,195,202
  biological studies, 74-5,150-2,164-7,170
Screening of populations, 151,176,197,203
Self-esteem (see Helplessness), 17,61
Sensitivity, 70,76,79,180,197,198
Sex chromosomes, 97,152
Sex differences,
  anxiety disorders, 94
  depression, 56,66,113
  personality disorders, 97,113
  research, 128-9
Skin conductance. See Electrodermal response
Sleep, 70-1,149
Smoking, 14,128,165-6,169-170
Social class, 112-3,186,190
  depression, 57,127
  personality disorder, 99,101
  schizophrenia, 48
Social mobility, 113
Social skills (see Coping skill), 34,90
Social support, 116-9,135
  community, 16,88
  family, 29,60,182
Specificity, 67,70,79,180,183,197-9
Stigma, 6
Sensation seeking, 98,165-9
Stirling County study, 5,120,190
Stress (see Life events), 47-8,117,118,122 131-9,142,169
Stress immunization, 89,134
Stress management, 89
Study design,
  comparisons, 12-15,17,194
  special-purpose, 143,163,188,203
Suicide, 114,166,168
Surveys (see Epidemilogic Catchment Area),
  current, 187,201
  historical, 5,190
  suitable variables, 38,186
  value, 103,128,175

Temperament. See Personality traits
Treatment, 49,71-2,85,87,88-9,153,155,189,
Twin studies, 43,46,86,91,146,148-9,150,16192

Virus infection, 47,187
Vulnerability (see Genetic factors),
  early events, 134,142,197
  genetic, 145,148-9,152-3
  personality, 61,91
  social learning, 134-5

Widows, 17,90

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